DISEASES OF THE HEART

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SECOND EDITION

W B SAUNDERS COMPANY

Philadelphia and London

Reprinted November 1956 and July 1957

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TO MY WIFE

AND

TO RICHARD AND BARBARA

PREFACE TO THE SECOND EDITION

The numerous advances in our knowledge of diseases of the heart since the first edition of this book have necessitated extensive rewriting of almost every chapter. However the basic objectives and the form of presentation of the first edition have been preserved.

A section of three chapters devoted to graphic methods of examination has been added because of the many recent contributions to this field.

Major sections of this revision have been devoted to cardiac surgery. New techniques of direct vision surgery such as inflow stasis, hypothermia, cross circulation, external shunts and pump-oxygenators, and the results of their clinical application have been included. The availability of surgical therapy for certain cardiac lesions has imposed new responsibility on the physician. Accordingly, appropriate presentations have been made of the application of the various diagnostic techniques, the interpretation of findings, the indications for surgery and especially the risks and results thus far obtained with available surgical procedures.

Extensive revisions and additions have been made to the sections on treatment other than surgical, throughout the book. These include among others the discussions of treatment of congestive heart failure particularly intractable heart failure, the discussions of digitalis, quinidine, Pronestyl and mercurial diuretics, the use of oral diuretics, very low sodium diets, resins, the induction of hyperchloremic acidosis with Diamox and ammonium chloride to potentiate the mercurial diuretics, the use of radioactive iodine in the treatment of intractable angina pectoris and intractable heart failure as well as of thyrocardiac disease, a discussion of the host of drugs that have been used in the treatment of angina pectoris, prophylaxis against rheumatic fever by the treatment and prevention of Streptococcus A (hemolyticus) infections, the treatment of rheumatic fever with corticosteroid hormones and the possibility of preventing cardiac damage, the modern antibiotic treatment of bacterial endocarditis including short term therapy, the control of tuberculous pericarditis with antituberculous drugs and the treatment of pulmonary (respiratory) and cardiac insufficiency in cor pulmonale according to the underlying pulmonary disease. The discussion of the treatment of acute myocardial infarction has been expanded particularly because of a more detailed consideration of the controversial questions of the use of anticoagulants, bed rest versus chair rest and the effectiveness of the vasopressor drugs in the treatment of shock. A number of new anticoagulants have been discussed as well as the use of Mephyton to control excessive hypoprothrombinemia or bleeding. The chapter on hypertensive heart disease has been greatly enlarged, partly because of the discussion of therapy, especially of the various newer hypertensive drugs.

The chapters on coronary atherosclerosis, congenital heart disease, chronic pulmonary heart disease have been greatly expanded. Extensive revisions or additions have been made in regard to the following subjects among others: the pathophysiology of cardiopulmonary disease, lung volumes and tests of pulmonary function, the viscoelastic properties of the lungs, the work and force of breathing, the relation of lipids and lipoproteins of cholesterol metabolism, of cholesterol and fat intake and of sex hormones to coronary atherosclerosis, cardiac arrest, the use of cardiac massage, defibrillation, the external cardiac pacemaker and defibrillator, Starling curves of cardiac function, vectorcardiographic findings in cardiac hypertrophy, bundle branch block and myocardial infarction, extracellular and intracellular electrolytes and electrolyte disturbances in congestive heart failure, recent contributions to the theories of the arrhythmias and Wolff-Parkinson-White syndrome, the varieties of syncope, diagnostic tests for pheochromocytoma, revised criteria for the early diagnosis and treatment of bacterial endocarditis and hyperserotoninemia.

My indebtedness is acknowledged to my colleagues on the Attending and Resident Staff of The Mount Sinai Hospital, New York, for the knowledge gained in many fruitful discussions, to various members of the Cardiographic Department and of the Catheterization Group for their aid in obtaining additional illustrations and to members of the Library Staff for assistance in obtaining medical journals To my wife without whose help this revision could not have been completed, I am indebted for aid in the preparation and reading of the manuscript, for typing my often illegible revisions, for checking the revised bibliography and its accurate reflection of additions and deletions in the text, for finding lost page numbers initials and even authors, for proper changes in the order and numbering of the bibliographic references and typing them, for reading the galley and page proof and for rearranging and typing the new index To my publishers The W B Saunders Company, I am grateful for their encouragement and cooperation

CHARLES K FRIEDBERG

New York City,

PREFACE TO THE FIRST EDITION

This book endeavors to provide a comprehensive and integrated exposition of the diseases of the heart The swift pace of recent advances in this subject calls for a reorientation in presentation, and a modification in emphasis from that found in available standard works on cardiac disease

In particular, special emphasis has been placed on the pathologic physiology of cardiac disorders, including the pathogenesis or mechanism of the symptoms and signs of circulatory failure, of angina pectoris and myocardial infarction and of the various manifestations of the individual cardiac diseases These discussions are not exhibited for mere academic consumption, but with the belief that an understanding of the dynamic events responsible for clinical phenomena is essential for maximum skill in diagnosis and treatment

The increased utilization of quantitative measurements in the clinical study of circulatory disease is reflected in detailed discussions of the cardiac output, blood volume and extracellular volume peripheral and intracardiac blood oxygen concentration and intracardiac pressures, body fluid and tissue electrolytes, and renal and pulmonary blood flow Throughout the book these measurements are applied to clinical understanding and practical usage in the every-day diagnosis and treatment of cardiac disease

Certain subjects of predominant importance have been presented as individual monographs Ten chapters have been devoted to circulatory failure, eight chapters to diseases of the coronary circulation and three to rheumatic fever and rheumatic heart disease Bacterial endocarditis has been discussed extensively because it is the most frequent curable cardiac disease Its bacteriological aspects have been presented in some detail because of their importance for effective diagnosis and treatment Congenital heart disease has likewise been fully described because of the many recent advances in diagnosis and treatment Special recognition has been given to cardiac catheterization, oxygen and pressure studies and angiocardiography as aids to the exact diagnosis essential for possible surgical treatment The diagnosis and treatment of other remediable cardiac conditions have been emphasized, e g , thyrocardiac disease, constrictive pericarditis and heart failure due to anemia avitaminosis arteriovenous aneurysm and myxedema Reference is also made to very recent advances in the surgical treatment of various clinical and experimental cardiac lesions including coronary artery disease valvular disease and septal defects as well as other congenital anomalies tumors and traumatic disturbances To avoid repetition, no special chapter is devoted to cardiovascular emergencies, but appropriate discussions may be found rapidly by reference to the individual conditions under the heading "emergencies, acute cardiovascular in the index

Certain less common forms of cardiac disease have been described in greater detail than is usually found in standard books, e g cardiac disease related to endocrine, metabolic and nutritional disturbances, including also the cardiac effects of hemochromatosis von Gierke's disease xanthomatosis, amyloidosis and acute porphyria Ample consideration has been given to the effects of various infections on the heart to nonspecific myocarditis and to other myocardial diseases of obscure origin, e g idiopathic hypertrophy scleroderma and myotonia atrophica

Roentgenology and electrocardiography have become essential elements of cardiologic practice and are thoroughly discussed throughout the book Individual chapters devoted exclusively to a formal presentation of electrocardiography and roentgenology have been omitted partly to avoid duplication and save space but chiefly because as isolated subjects they could not be presented adequately in single chapters Instead emphasis has been placed on the application of electrocardiographic and roentgenologic interpretation to clinical practice, in which these findings mi

be integrated with the clinical history, symptomatology and other objective data

Electrocardiography has been discussed in detail in connection with the arrhythmias, angina pectoris, myocardial infarction, pericarditis and myocardial disease, while both electrocardiography and roentgenology including angiocardiography have been amply considered in connection with such subjects as chamber enlargement, valvular heart disease and congenital cardiac lesions To a lesser extent electrocardiographic and roentgenologic findings are also described in connection with almost every other type of heart disease, according to the importance and diagnostic value of these findings relative to other clinical features A number of other graphic methods, including phonocardiography roentgenkymography electrokymography (fluorocardiography) and endocardial electrocardiography, have recently received increasing attention from cardiac investigators and these have been briefly mentioned when pertinent However, because of their limited practical value at the present time these and other subjects in which the author may have a special interest have not been unjustly emphasized

It is impossible to make specific acknowledgment to the host of individuals who directly or indirectly have helped provide the knowledge which is the basis for this book I owe much to hospital colleagues and associates, and especially to Dr Arthur Fishberg Of the numerous teachers and collaborators to whom I am indebted I wish to mention specifically the late Dr C J Rothberger of Vienna who trained me in experimental cardiology and electrocardiography, the late Dr Louis Gross in cardiac pathology and the late Dr Emanuel Libman in clinical cardiology

For the opportunity of studying and utilizing the clinical material on his wards and for his encouragement in clinical research, I am especially grateful to Dr George Baehr I also wish to offer thanks to Dr B S Oppenheimer and Dr I Snapper, under whom I have served for brief periods Dr A Master kindly permitted my use of the electrocardiographic files and Dr M Sussman permitted the use of the roentgenologic files of The Mount Sinai Hospital I am grateful to Drs A Grishman and Joan J Lipsay for their assistance in choosing most of the material for illustrations and to Drs J B Schwedel and R H Marshak for isolated roentgenograms To my wife I am indebted for typing the original manuscript and its several revisions, for editorial assistance and especially for her tolerance during my writing of this book

The editorial and administrative staffs of my publisher the W B Saunders Company, have been helpful and cooperative

CHARLES K FRIEDBERG

New York City

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PART I

GRAPHIC METHODS OF CARDIAC EXAMINATION

Chapter 1

ROENTGENOLOGIC EXAMINATION OF THE HEART

Roentgenologic examination of the heart is one of the major diagnostic techniques in clinical cardiology and is essential for complete cardiac evaluation. Not only does it provide an accurate outline of the projected cardiac borders but it reveals also the volume of the heart and its vascular extensions, the relative size of the individual chambers, the character and extent of the cardiac pulsations and the presence of intracardiac or pericardial calcification. By rotating the patient the examiner may view the heart from every angle. Permanent objective records of the cardiac silhouette and the pulsations of its borders may be made on films or tracings. Serial records at varying intervals may reveal significant changes in size, contour or pulsation of the heart and thus provide useful information as to the course and progression of various cardiac diseases.

ROENTGENOLOGIC TECHNIQUES

The roentgenologic techniques most commonly employed in examination of the heart are fluoroscopy and teleoroentgenography or orthodiagraphy. But in special instances or for research purposes these are supplemented by angiocardiography, kymography or electrokymography, tomography (planigraphy), cinematofluorography and volumetric reconstructions. Technical details can be mentioned only briefly in this chapter and the reader is therefore referred to the excellent monographs of Assmann,[2] Vaquez and Bordet,[20] Zdansky,[illegible] Roesler,[illegible] Laubry et al.[illegible] and Schwedel.[illegible] The anatomic basis for the roentgenologic silhouette of the heart is presented in a monograph by Koch and Weck.[illegible]

FLUOROSCOPY

This permits direct and continuous roentgenologic examination of the heart. The examiner is in front of the fluorescent screen and the patient behind the screen, between the screen and the x-ray tube. The screen and tube are rigidly connected and move as a unit. By varying the horizontal and vertical dimensions of the aperture one may alter the size of the image on the screen so as to view the entire chest or to concentrate on small areas. Because of the proximity of the patient to the tube, the roentgen rays diverge considerably and thus exaggerate the size of the heart. Therefore fluoroscopy is not used for exact measurement of the cardiac dimensions, but it provides a sufficiently accurate approximation to permit the recognition of generalized or chamber enlargement, as well as alterations in the pulsations of the heart and great vessels. Various devices have been suggested to correct for fluoroscopic enlargement of the true cardiac size.[7] The silhouette is studied not only with the patient facing the screen (posteroanterior position) but also in various degrees of rotation, especially in the right anterior oblique and left anterior oblique positions,[12] which will be described below. Because of the simplicity, convenience and economy of fluoroscopy, this technique has become a routine part of the cardiac examination in the physician's office as well as in the clinic or hospital.

Fluoroscopic examination is often conducted while the patient swallows a thick solution of barium sulfate in order to determine more clearly enlargement or abnormal pulsation of the left atrium or of the aorta. Anomalies of the aortic arch may be disclosed by their effect on the barium-filled esophagus. Fluoroscopy is used to facilitate the passage of a cardiac catheter and to localize the position of the catheter tip. It is the basis of the technique of electrokymography (fluorocardiography).

Cinematofluorography is the technique of recording the image on the fluoroscopic screen by photography.[3, 16] A method has also been

developed to obtain three dimensional visualization of cinefluorographic films by the use of two synchronized x ray tubes [17]

It is essential that the physician engaging in fluoroscopic examinations should be mindful of the hazards of roentgen ray exposure These dangers may be minimized by limiting exposure to the briefest possible duration This in turn requires maximal accommodation (dark adaptation) of the examiner The area of exposure is reduced by apposing the screen to the chest wall and by narrowing the aperture The examiner should be protected by the use of a leaded screen, chair apron gloves and goggles

TELEOROENTGENOGRAPHY

An x ray film (roentgenogram) of the chest is taken at a standard distance, usually 2 meters or 6 feet At this distance the x rays are much less divergent than at the close range of fluoroscopy and the degree of exaggeration of the size of the cardiac silhouette is usually not more than 5 or 10 per cent Usually a film in the posteroanterior position is taken with the patient's anterior chest wall in contact with the film containing cassette and the roentgen ray tube centered at the level of the sixth thoracic vertebra Other views may also be filmed corresponding to those mentioned under fluoroscopy Because of variations in the cardiac silhouette with respiration and motion of the diaphragm the same standard exposures are made, usually at the end of a normal inspiration For more accurate research studies the exposure may be synchronized with systole and diastole

ORTHODIAGRAPHY

In order to avoid the exaggerating effect of divergent x rays and thus obtain more accurate measurement of heart size, only the central parallel rays of the x ray tube are used in orthodiagraphy The fluoroscopic screen is fixed and the patient stands behind the screen The aperture is narrowed so as to leave a very small square slit through which the x rays cast an image on the screen The tube and aperture are moved together along the outlines of the chest wall diaphragms and cardiac chambers on the fixed screen The examiner rapidly traces these outlines by pencil or crayon on transparent paper attached to the front of the screen The slightly greater accuracy permitted by this method is outweighed by the greater need for skill and the greater time consumed

THE NORMAL CARDIAC SILHOUETTE

For purposes of simplification and standardization we employ three views which usually yield adequate information as to the shape, size and (by fluoroscopy) the pulsations of the heart These views are the posteroanterior the right oblique anterior and the left oblique anterior Occasionally the lateral view is also of value

The Posteroanterior View

About two thirds of the cardiac shadow is to the left, and one third to the right of the mid line (Fig 1) The *right border* is composed of three contours, which from above downward are (1) The *innominate vein* and its continuation into the superior vena cava (2) The *superior vena cava* or, in older individuals, the *ascending aorta* The shadow of the ascending aorta may be seen within that of the superior vena cava even when it does not reach the right border of the heart (3) The *right atrium* which forms a well curved contour separated by a slight indentation from the superior vena cava or aorta and is the largest salient of the right border of the heart Occasionally there may be seen a small portion of the shadow of the inferior vena cava as it enters the lower region of the right atrium

The *left border* also has three main contours which are formed from above downward by (1) The aortic arch continuing into the descending aorta (*aortic knob*) (2) The *pulmonary artery salient* This is composed of the pulmonary artery and its left main branch The left atrial appendage may appear below the pulmonary artery This middle segment is sometimes referred to as the waist of the heart because it is distinctly indented as compared with the bulge of the third contour below it The junction of the pulmonary salient and the latter contour is denoted by a reversal in direction of pulsation the pulmonary salient moving outward while the left ventricular contour moves inward during ventricular systole (3) The *left ventricle* This forms a prominent convex contour, which extends well into the left pulmonic field and curves downward and back toward the mid line to cross the shadow of the left leaf of the diaphragm In the left cardiodiaphragmatic angle there is often a faint triangular shadow

which represents a pad of fat in a fold extending from the pericardium to the mediastinal and diaphragmatic pleura Failure to recognize the cause of this shadow may lead to error in measuring the cardiac size

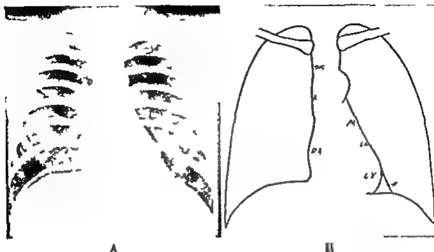


Fig 1 A Normal cardiac silhouette Male aged 45 Posteroanterior view
B Diagram of *A* RA = right atrium Ao = ascending aorta SVC = superior vena cava LV = left ventricle LAp = left atrial appendage PA = pulmonary artery F = apical fat pad.

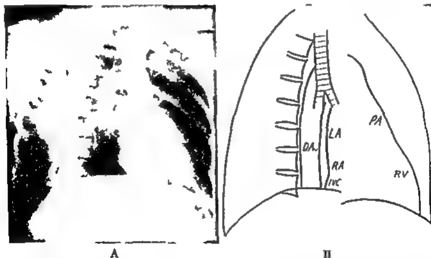


Fig 2 *A* Normal heart Same as in Fig 1 Right anterior oblique view
B Diagram of *A* IVC = inferior vena cava DAo = descending aorta RV = right ventricle LA = left atrium. Other abbreviations as in Fig 1*B*

The Right Anterior Oblique View

The patient facing the screen is rotated anteriorly so that his right shoulder is turned forward toward the screen The angle formed by the shoulders with the screen should be about 30 to 40 degrees for study of the aorta, or 50 to 60 degrees for study of the left atrium The patient s right hand is placed on his head and the dorsum of his left hand is placed on the crest of the ilium, the left elbow being drawn forward at the same time The *anterior border* of the cardiac silhouette in this view (Fig 2) is formed in its upper third by (1) *the ascending aorta and arch* and in its lower two thirds by (2) *the pulmonary artery and* (3) *the right ventricle* With only moderate rotation (30) the left ventricle forms the lower anterior contour

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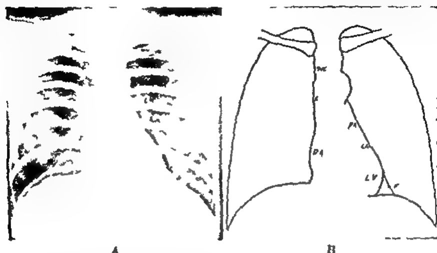


Fig 1 *A* Normal cardiac silhouette Male aged 43 Postero anterior view
B Diagram of *A* RA = right atrium Ao = ascending aorta SVC = superior vena cava LV = left ventricle LAp = left atrial appendage PA = pulmonary artery F = apical fat pad.

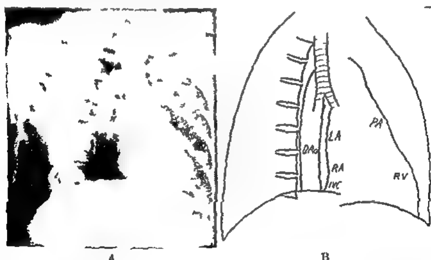


Fig 2 *A* Normal heart Same as in Fig 1 Right anterior oblique view
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ette from above downward reveals the following structures (1) *The trachea and left main bronchus* form a transparent band, overlying which is the right branch of the pulmonary artery and the superior vena cava (2) *The descending aorta,* which appears as a pale vertical band between the spine posteriorly and the denser posterior cardiac border anteriorly (3) *The left atrium* which is slightly convex and forms the major portion of the posterior cardiac border (4) *The right atrium* with the shadow of the inferior vena cava entering it From posterior to anterior the atrium, and the left ventricle [11, 10] The *anterior aspect* of the cardiovascular silhouette in this position (Fig 3) is composed from above downward as follows (1) *The ascending aorta,* which may be overlapped above by the innominate vein and superior vena cava (2) The *right atrial appendage* which is directed upward and posteriorly, forming an oblique or sometimes almost horizontal segment (3) *The right atrium,* which forms most of the anterior cardiac contour in this view According to angiocardiographic studies the right ventricle may constitute the lowermost

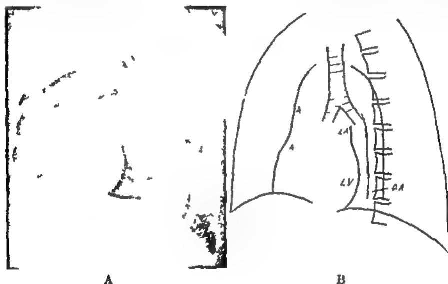


Fig 3 *A* Normal heart. Same as in Figs 1 and 2 Left anterior oblique view *B* Diagram of 3 *A* Abbreviations as in Fig 2*B*

diaphragmatic surface is formed by the inferior vena cava, right atrium and right ventricle

In the right anterior oblique view, the barium filled esophagus is seen between the posterior cardiac border and the descending aorta running an essentially vertical course, but slightly concave anteriorly, with a shallow indentation by the aorta and right bronchus

The Left Anterior Oblique View

The patient is rotated anteriorly so that his left shoulder is toward the screen The angle of rotation is 40 to 50 degrees for study of the aorta, and 50 to 60 degrees for study of the ventricles The patient s left hand is placed on his head, his right hand on his right hip and his right elbow drawn forward This view is especially valuable for the study of the aorta the inflow tract of the right ventricle the left portion of this contour, but most often it is obscured by the right atrium [19] As the body is rotated from the oblique toward the lateral, the right ventricle forms the major portion of the lower contour anteriorly

Along the superior margin the aorta may be followed craniad where it arches over the top of the cardiovascular silhouette and continues into the descending aorta which merges with the shadow of the spine Below the aortic arch is the bifurcation of the trachea forming a transparent region known as the aortic window, traversed by the left pulmonary artery [11] The left main bronchus normally forms an angle of less than 45 degrees with the direction of the trachea

The dorsal aspect is formed in its upper third by (1) *the left atrium,* and in its lower two thirds by (2) *the left ventricle* The cardiac shadow posteriorly should be separated from

the spine if the patient is rotated 45 degrees or more The lower (diaphragmatic) border of the cardiac silhouette is important in this view as it may reveal enlargement of the inflow tract of the right ventricle The anterior two thirds or three quarters of this border represents the diaphragmatic surface of the right ventricle The posterior quarter is formed by the left ventricle Between these two there is often a small indentation which is best seen during deep inspiration and in systole This indentation was said to represent the interventricular sulcus[19] but it does not correspond to the interventricular septum as seen by angiocardiography [19]

As the patient is rotated into a *lateral position* the anterior contours from below upward are the right ventricle and its conus the pulmonary artery and the aorta Posteriorly the left ventricle forms the lower contour and the left atrium the upper

Factors Modifying the Normal Cardiac Silhouette

The appearance of the cardiac silhouette has a considerable range of normal variation depending chiefly on body type (hypersthenic sthenic and asthenic) and on the phase of respiration and the position of the diaphragm but also on age sex height weight and the phase of the cardiac cycle These factors must be considered in evaluating the fluoroscopic findings

In *hypersthenic individuals* with a short, broad rounded chest and elevated diaphragm the cardiac shadow tends to be short wide and situated transversely and the apex appears to be displaced to the left The pulmonary artery segment is relatively short and forms a distinct indentation (waist) with the long prominent left ventricular contour of which the lower portion is often obscured by the diaphragm or fat pad Similar transverse position of the heart simulating left ventricular enlargement may be due to a high diaphragm e g in deep expiration with hepatic enlargement and ascites during pregnancy and in obese subjects with meteorism Scoliosis even the slight scoliosis commonly seen in children produces an apparent enlargement of the cardiac shadow because most of the heart lies to the left of the spine [1] A similar effect is produced by a funnel chest (p 981)

In *asthenic individuals* with a long flat narrow chest, the cardiac silhouette is long and narrow and its major contours only slightly convex In its extreme form this type of heart is pear-shaped, centrally located and is termed the cor pendulum or drop heart The pulmonary artery segment is relatively long and prominent, even in the postero anterior view but more so in the right anterior oblique view, in which it may simulate the appearance seen in right ventricular (pulmonary conus) enlargement A vertical cardiac shadow tends to occur during deep inspiration in the erect as compared with the recumbent position, and in the presence of pulmonary emphysema In infants and very young children the cardiac shadow is centrally located but unlike the drop heart appears globular with equal extent and prominence of its cardiac borders to the right and left of the spine

For Measurement of Cardiac Size etc see p 99

CARDIAC TOMOGRAPHY

Tomography (planigraphy laminography sectional radiography) is a roentgenologic method by which serial layers or planes of the body are examined The desired frontal sagittal or other plane at any body depth is clearly portrayed while other planes, superficial or deep to this plane are blurred out and do not obscure the desired plane Inasmuch as the individual cardiac chambers and the great vessels are located predominantly in different planes tomography of the chest can be utilized to examine individual structures of the heart and vascular pedicle without obscuration by overlying or subjacent cardiac chambers or other structures [21 6]

Tomography is accomplished by having the focal point of the roentgen ray tube move in one direction while the film on the other end of the same axis moves simultaneously in the opposite direction [1] The center of this axis which may be raised or lowered is at the level of the body plane to be examined That plane remains constant with respect to the axis of the x rays and its projection on the film and is clearly depicted, while the other planes photographed successively by the moving tube are blurred out because they are in motion and appear on different portions of the film The chief disadvantage is that multiple sections must be studied involving considerably more time and expense than conventional radiography

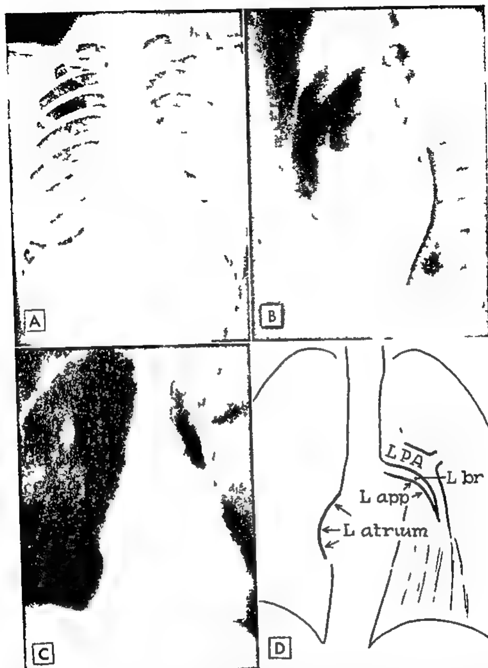


Fig 4 4 Conventional posteroanterior roentgenogram of the chest of a 32 year old woman with mitral teno is Left lower contour displaced to left Prominent pulmonary arteries Prominent left atrial appendage (left middle contour)

B Left lateral view of same showing left atrium indenting barium filled e ophagus

C Tomogram (posterior section) of same Enlarged left atrium protruding on to right border Left atrial appendage elevating left stem bronchus and left pulmonary artery Ab ence of prominent left lower contour because apex is formed by enlarged right ventricle which is seen in anterior sections Left ventricle seen in this posterior section is not prominent or enlarged

D Tracing of C

It has been claimed that cardiac tomography may aid in the differential diagnosis between mitral stenosis and mitral insufficiency, and between aortic or pulmonic insufficiency combined with mitral stenosis, by distingui hing left from right ventricular enlargement Hypertrophy and dilatation of the right ventricle is disclosed by enlargement

of the right ventricular shadow in anterior planes with disappearance of this enlarged shadow in posterior sections Left ventricular hypertrophy is indicated by the presence of an enlarged ventricular shadow in posterior planes

Left atrial enlargement has been shown clearly by tomography (Fig 1)[14] Patent ductus arteriosus has been revealed as a distinct vascular shadow in a median plane of a lateral projection of the thorax Tomography is said to outline clearly coarctation of the aorta in a suitable plane of the left anterior oblique projection Calcification of the mitral or aortic valve is more clearly depicted by cardiac tomography than by conventional roentgen ray films or fluoroscopy Aneurysms of the aorta or pulmonary artery may also be clearly disclosed

The cardiac volume has been determined by axial tomography i e by films of about a *dozen parallel cardiac planes perpendicular to* the long axis of the subject and a known fixed distance apart[4, 8] The cardiac areas in the various sections are measured and the volumes calculated by multiplying by the distances between sections

ROENTGENKYMOGRAPHY AND ELECTROKYMOGRAPHY

Roentgenkymography

This is the technique of recording the pulsations of the cardiac borders by means of roentgen rays The latter are directed at moving film which comes in contact with a stationary grid with vertical and horizontal slits The borders of the cardiac silhouette do not appear as smooth outlines, but have a horizontal picket fence conformation representing the successive positions of the border in diastole (outward) and systole (inward) Roentgenkymography has been employed infrequently as a possible aid in the differentiation of pericardial effusion from cardiac enlargement and in the study of myocardial infarction and ventricular aneurysm It is of little if any clinical importance at the present time[■]

Electrokymography

This is a method which employs a photoelectric device for the graphic representation of the movements of the cardiac borders as they appear on the fluoroscopic screen[28, 29, 31] A multiplier type of photosensitive tube containing *a rectangular slit covered by a small* fluorescent screen directly over the sensitive surface of the tube is attached to the patient's side of the conventional fluoroscopic screen perpendicular to the cardiac border which is being studied As the heart is projected on the fluorescent screen outward (lateral) movement of the cardiac border partially obstructs the slit and reduces the beam of x rays This in turn reduces the amount of fluorescent light affecting the photosensitive tube and the strength of electric current emitted Conversely an inward (medial) movement of the cardiac border increases the intensity of the beam of x rays and of fluorescent light and thereby the amount of electrons generated by the phototube

When the photosensitive tube is so placed as to be affected by x rays passing through the cardiac structures rather than through its borders, changes in cardiac density result in corresponding changes in the intensity of the *x ray beam and in the current generated by* the photosensitive tube which are inversely proportional to the posteroanterior thickness of the organ (densimetry) The resulting current of varying intensity is suitably amplified and recorded as a phasic curve by an electrocardiograph The polarity is arranged so that an outward (lateral) movement of a cardiac border or an increase in density of a cardiac chamber produces an upward deflection in the electrokymographic curve (EKY) while an inward (medial) movement of a cardiac border or a diminution in cardiac density causes a downward deflection

For purposes of timing and as a reference frame for the events of the cardiac cycle the EKY is taken simultaneously with tracings of the carotid pulse[6] and heart sounds[9] or electrocardiogram[■] or with simultaneous electrocardiogram and pressure pulses of the right ventricle and pulmonary artery (by cardiac catheterization)[24] There is a time lag of 0 015 to 0 025 sec in recording by the EKY The subject standing behind the fluoroscope screen, may be placed in any desired position e g the posteroanterior, right anterior oblique and so on Studies are usually made of the ventricles,[■] the atria[5] the aorta and pulmonary artery[6] and *if desired* of the peripheral pulmonary arteries It may also be used to study the pulsation of suspected aneurysms

A normal electrokymogram is depicted in *Figure 5*

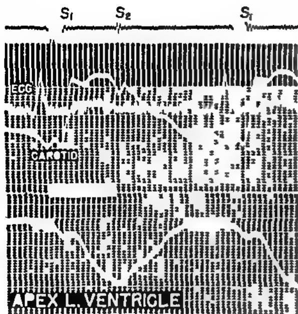


Fig 5 Normal ventricular electrokymogram from border of apex of left ventricle Downward limb and trough during systole opposite in direction to upward limb and crest of simultaneous carotid pulse

Evaluation of Electrokymography

Electrokymography is of very limited practical value in clinical cardiology At present it is employed essentially in research *It has been utilized chiefly in an attempt to* shed more light on the mechanical changes of the heart in the various phases of the cardiac cycle, including isometric contraction and relaxation Physiologic studies have also been *made of the effect of drugs on the mechanical* behavior of the heart

More or less characteristic patterns have been noted in a variety of clinical conditions, but almost always these abnormalities can be detected more simply and with greater certainty by other means Electrokymography is most likely to be useful in those cardiac diseases which *result* in *localized* cardiac damage or gross impairment of cardiac filling and contraction

A characteristic electrokymographic pattern has been found in constrictive pericarditis (Fig 6) The electrokymogram may disclose distinctly abnormal asynchronism in ventricular contraction in cases of bundle branch block [27] A reversal of the normal ventricular EKY pattern may be demonstrated at the border of infarcted myocardium (Fig 7) or the site of a ventricular aneurysm [8] In congenital heart disease high amplitude in pulmonary *artery electrokymograms* may be disclosed in cases of high pulmonary artery pressure, e g

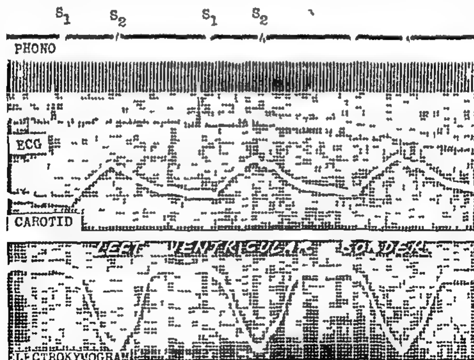


Fig 6 *Electrokymogram left ventricular border in constrictive pericarditis Alternate V and flat-top curve* Flat-top (plateau) represents impaired diastolic filling in first part of horizontal segment isometric contraction in latter portion Down stroke of V represents ejection upstroke isometric relaxation and early diastole

interatrial septal defect and low amplitude in cases of pulmonary stenosis, especially over the peripheral lung fields. A sharp anacrotic notch in the aortic electrokymogram is observed in cases of subaortic and aortic stenosis. More or less distinctive findings in mitral and tricuspid valvular disease have been recorded.

There are a number of limitations to the value of electrokymography imposed by the method itself. There is considerable variation in normal patterns, the range of which has not been satisfactorily defined. The observed pattern may differ with change in the site of application of the electrokymograph slit on a given chamber segment. The effect of alteration of cardiac volume during the cardiac cycle is modified by superimposed positional changes. Considerable difficulty arises in attempts to correlate various portions of the EKY curves with the different phases of cardiac cycle, for even with the use of simultaneous carotid pulse tracings, phonocardiograms and electrocardiograms there is disagreement in points of reference for the beginning and end of the different cardiac phases.[31]

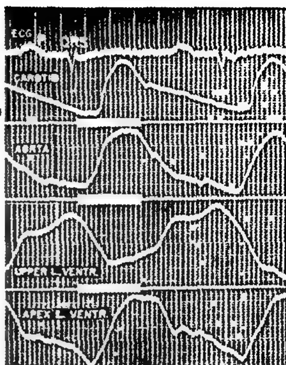


Fig. 7. Electrokymogram in myocardial infarction. Reversal of pulsation at apex of left ventricle. Paradoxical (outward) pulsation of apex shown by upstroke and crest during systole in opposite direction to upper border of left ventricle and same direction in simultaneous carotid pulse. Compare Fig. 5.

ANGIOCARDIOGRAPHY

Angiocardiography is the roentgen ray method of portraying the cardiac chambers and great vessels and the course of the blood flow in these structures by opacification with an intravenously injected radiopaque solution.[34, 39, 40]

Radiopaque Contrast Substances

The contrast substances usually employed are *Diodrast* (iodopyracet) in 70 per cent solution, *Neo-iopax* (uroselectan B sodium iodomethamate) in 75 per cent solution and more recently *Urokon* (sodium acetrizoate) in 70 per cent solution.[39] These solutions contain between 44 and 52 per cent of iodine. The *dose* is usually 1 cc. of the contrast solution per kg. body weight in infants and young children with a maximum of 15 cc. Adults are given 40 to 50 cc. and children intermediate doses between 15 and 40 cc. according to their size.

Technique of Angiocardiography[40, 47]

The patient should be hospitalized, although adults may have the procedure as outpatients. Breakfast is omitted if the examination is performed in the morning and lunch is omitted if it is made in the afternoon. The patient is premedicated with a barbiturate one hour before the procedure. As a rule opiates are omitted, especially in cyanotic infants, but occasionally morphine sulfate (0.2 mg. per 10 lbs. of body weight) is desirable for angiocardiography in the infant. Codeine or Hycodan in small doses may be administered if necessary to inhibit a cough which may interfere with obtaining satisfactory films. Penicillin may be given prophylactically. General anesthesia is administered to infants, young children and all others who cannot otherwise cooperate.

The *injection of the contrast material* is performed in a room equipped for roentgen ray examination. Control films are first made in the same projections as will be used for angiocardiography. These are developed and inspected before injection of the contrast material.

A suitable antecubital vein, or occasionally a cephalic vein at the wrist, is chosen for injection in adults and the saphenous or external jugular vein in young children. Under sterile precautions a cut-down is made over the vein through a procaine wheal and

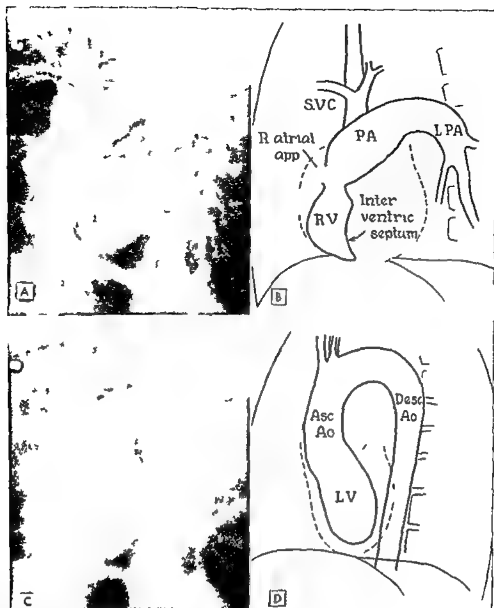


Fig 8 1 Angiocardiogram of right heart and pulmonary arteries Left anterior oblique view two seconds after injection
B Tracing of *A*
C Angiocardiogram of left heart and aorta Left anterior oblique view seven seconds after injection
D Tracing of *C*

special needle with a stopcock unit or plastic tube is inserted into the vein and kept in place with adhesive The patient is positioned as desired usually in the left anterior oblique or posteroanterior position After it is determined that there is a free flow into the vein the syringe containing the radiopaque contrast solution is attached to the needle The injection is made rapidly as the patient starts a deep inspiration and is completed in two seconds The first roentgen ray exposure is made while the patient holds his breath in full inspiration Rapid serial angiocardiographic films are then made with the aid of the Fairchild automatic roll film magazine, which yields films at the rate of about two exposures per second

Side Actions and Dangers of Angiocardiography

Angiocardiography is usually an unpleasant

experience for the patient Following Diodrast, there is a bitter or metallic taste in the mouth, after which a sense of heat pervades the entire body but usually subsides within five or ten minutes Weakness is common Dizziness nausea, vomiting urticaria and occasionally syncope or shock may occur There may be a transient febrile reaction several hours after the injection Thrombosis of the injected vein occurs very frequently Deaths have occurred in more than 20 acknowledged cases

After Neo-iopax there is an initial sense of heat followed by a throbbing headache which may be inten e Weakness and thirst are common complaints Flushing or pallor is often noted Nausea thrombosis of the injected vein and syncope may occur as commonly as after Diodrast Cough after 5 to 8 seconds while the pulmonary capillaries are filling is not uncommon and may interfere with exposures during filling of the left ventricle Death after Neo-iopax is probably rare The reactions after Urokon appear to be milder as well as less unpleasant to the patient than after Diodrast or Neo-iopax

Tachycardia is usual after the injection The blood pressure may fall at first but then there is a marked rise in systolic and pulse pressure The hypotensive reaction is most prominent after Diodrast Electrocardiograms may disclose premature ventricular contractions and other arrhythmias[19] prolongation of the Q T interval and diphasic or inverted T waves The ballistocardiogram may be quite abnormal

Goodwin et al[44] reported 2 deaths among 118 cases but neither was directly attributable to the angiocardiography Dotter and Jackson[19] reported a case fatality rate of 0 4 per cent in 6739 cases of all types

Structures Depicted in Successive Angiocardiograms

Examination of the successive angiocardiographic films taken at definite recorded intervals after injection reveals not only the size, position and configuration of the various vessels and cardiac chambers but especially the sequence and time of filling of these structures[5, 18] At one second the right atrium and its appendage are filled and by two seconds the right ventricle and usually also the pulmonary arteries (Figs *8A*, *9A*) At three seconds the right atrium is fading and by four seconds is empty, whereas the right ventricle may be seen in diastole By six to eight seconds after injection, the contrast material normally has left the right side of the heart and opacifies the left atrium The left atrial appendage is usually not well visualized, but the pulmonary veins may be observed entering the left atrium By seven to nine seconds the left ventricle and aorta are also opacified (Figs *8C*, *9C*) The interventricular septum is seen to be convex to the right The thoracic aorta and the arteries arising from the arch are best studied in the left anterior oblique view

Indications for and Value of Angiocardiography

Angiocardiography is most commonly indicated in cardiologic practice (1) in certain cases of congenital heart disease (2) in distinguishing aneurysms of the great vessels from pulmonary or mediastinal tumors (3) in the diagnosis of suspected pulmonary arteriovenous fistula (4) in determining the nature of cardiac or paracardiac shadows e g ventricular aneurysm or aneurysm of the sinus of Valsalva versus intrinsic pulmonary lesions (5) in differentiating pericardial effusion from cardiac enlargement

Angiocardiography may be desirable for the surgeon not only in providing or confirming the diagnosis of a congenital cardiac lesion, but also in disclosing or excluding associated anomalies and in revealing the size position and configuration of structures which may be important in the surgical procedure[43] However since angiocardiography is a relatively formidable unpleasant and occasionally dangerous procedure, its performance should be clearly justified by the value of the information which it is expected to provide It should be performed only after simpler conventional methods of study, including cardiac catheterization if necessary, have failed to provide an adequate basis for undertaking or rejecting a surgical procedure or if the surgeon requires a more exact delineation of the cardiac or vascular abnormalities Angiocardiography may clearly depict some but not all of the anomalies of a given congenital cardiac syndrome, and occasionally its findings are misleading unless they are carefully correlated with clinical roentgenologic electrocardiographic and catheterization studies

Angiocardiography is most likely to be employed in young cyanotic infants in whom an exact diagnosis is uncertain after conventional

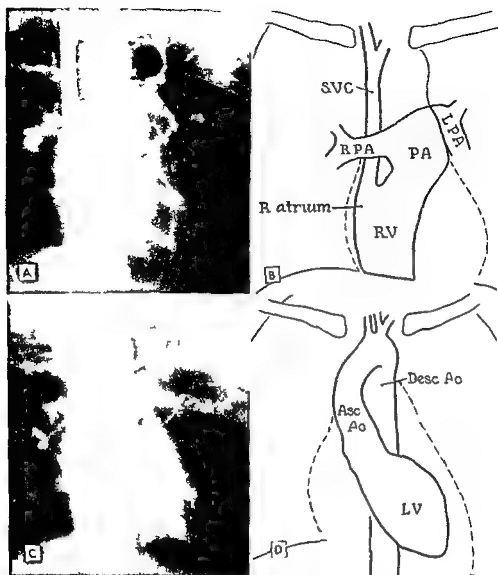


Fig 9 4 Angiocardiogram of right heart and pulmonary arteries Posteroanterior view two seconds after injection
B Tracing of *A*
C Angiocardiogram of left heart and aorta Posteroanterior view seven seconds after injection
D Tracing of *C*

clinical and laboratory examinations, and in whom cardiac catheterization is not diagnostic or cannot be performed But angiocardiography is al o most dangerous in this group It may not be essential for the diagnosis of tetralogy of Fallot, but it may help the surgeon in demonstrating the position and number of the great vessels and other anatomic features It differentiates Fallot s tetralogy from pulmonary stenosis with right-to-left shunt through the atrial septum Angiocardiography is es ential for the diagnosis of complete transposition of the great vessels or the Bing Taussig heart It also discloses the presence or absence of a pulmonary artery in cases of pulmonary atresia and the source and nature of blood supply to the lungs Similarly angiocardiography not only confirms a clinical diagnosis of tricuspid atresia but indicates that there is under vascularization of the lungs and reveals whether there is a pulmonary artery which can be used for a Blalock operation Angiocardiography is diagnostic in cases of Ebstein s anomaly of the tricuspid valve and in truncus arterio us Although angiocardiog

raphy is usually diagnostic in cyanotic types of congenital heart disease with right to-left shunt it usually does not distinguish between a tetralogy of Fallot and the Ei enmenger complex nor is it diagnostic of patent ductus arteriosus with pulmonary hyper tension and reversal of shunt Cardiac catheterization is necessary in most of these cases Angiocardiography usually provides a preci e diagnosis of anomalous entrance of the pulmonary veins into the superior or inferior vena cava or right atrium

Angiocardiography is infrequently indicated in noncyanotic cases of congenital heart disease but it may be desirable in cases of coarctation of the aorta to delineate the na ture and extent of the constriction and the position of related vessels *Thoracic aortog raphy* provides an even more accurate pic ture Angiocardiography is rarely necessary and is less useful than cardiac catheterization in cases of interatrial or interventricular septal defect, pulmonary stenosis or patent ductus arteriosus but it may occasionally be desirable to determine the presence and na ture of associated defects Angiocardiography clearly depicts the presence and type of dextrocardia and the presence of dilatation of the pulmonary artery

Rapid Biplane Angiocardiography

This is a method of synchronous angio cardiography in two planes perpendicular to each other with a speed of 10 to 12 exposures per second[4] [illegible] It permits the study of the atria and ventricles in both systole and diastole Frontal and lateral exposures, or left and right oblique exposures are synchronized by a motorized table An electrocardiogram made during the procedure fixes the precise time between ex posures and registers the cardiac phase Because of the numerous exposures appro priate precautions must be taken to avoid radiation hazards Flash exposures should be used instead of uninterrupted irradiations Dotter[38] called attention to the value of short-duration roentgen exposures for angio cardiography to improve diagnostic accuracy and to avoid the expense of the multiple exposures and films required in rapid bi plane angiocardiography By the use of an electronically controlled grid operated electron tub in series with the diagnostic tube three millisecond clinical radiographic ex posures could be made

By the technique of rapid biplane angiocardiography it is possible to demonstrate more discretely than by conventional angiocardiography the normal and pathologic anatomy of the cardiac chambers and great vessels and to reveal information as to normal and abnormal cardiac dynamics [illegible] When placed side by side the films of two cardiac planes permit a three-dimensional apprecia tion of the capacity as well as configuration of the cardiac chambers The volume of indi vidual chambers can be estimated by simul taneous measurements of the cardiac sil houettes in the two perpendicular projections and the stroke volume by the difference of the calculated volumes in systole and diastole

Photofluorography (cineangiocardiogra phy) *may be used instead of direct roent* genography to obtain serial angiocardiograms[46] But although this may provide an increased rate of exposures the cin ma tographic projections lack the details and sharpness of direct angiocardiograms Fur thermore there is a much greater irradiation exposure of the patient with photofluorogra phy

Selective Angiocardiography

Selective angiocardiography is designed to improve the contrast visualization of various portions of the heart or great vessels by con centrating the contrast medium in the area to be studied[47] [illegible] The contrast medium, e g , 70 per cent Urokon (1 to 1 [illegible] ml /kg body weight), is injected through a catheter with the aid of a pressure apparatus Radiographs are taken in at least two planes at right angles to each other

In order to effect the visualization of the entire intrathoracic circulation the catheter tip is placed in the most proximal part of the subclavian or innominate vein The opening in the catheter is 5 cm from the tip To visualize the right atrium the tip of the catheter is placed in the lower part of the superior vena cava To visualize the right ventricle the catheter tip is situated in the pulmonary conus where it should be made to lie steady Stenosis of the infundibulum and of the pulmonary valves is thus distinctly visualized (Fig 10) In cases of suspected tetralogy of Fallot the catheter is placed in the aortic orifice and the contrast medium will visualize the aorta innominate carotid and subclavian arteries In addition since the catheter slips down into the right ventricle



Fig 10 Selective angiocardiography Pulmonic stenosis Man aged 45 *A* Systole Note dome-shaped stenotic pulmonic valve (white arrow) Jet (J) of contrast material forced through central orifice of stenotic pulmonic valve from infundibulum (I) into pulmonary artery (PA) CSV crista supraventricularis

B After pulmonary valvulotomy Broad jet of contrast medium now spurts through dilated opening Infundibulum is widened (From Kjellberg et al Diagnosis of Congenital Heart Disease Yearbook Publishers Inc)

during the injection the right ventricle pulmonary conus and pulmonary artery are visualized

Fluoroscopic Image Amplification

This apparatus represents a major advance in diagnostic roentgenology and overcomes many of the deficiencies of cardiac catheterization and angiocardiography It particularly enhances the value of combined cardiac catheterization and selective angiocardiography

The image amplifier increases the brightness of the fluoroscopic image more than 1000 times (Philips) and permits visualization of mediastinal structures in a lighted room Two observers may study the amplified image simultaneously through attached optical periscopes The amplified image can be photographed or scanned by a television camera and reproduced on a television screen, or photographed at 18 to 64 frames per second with a 35 mm motion picture camera and then projected in slow motion for study At present commercial equipment is limited to a field diameter of about 12 cm but this is adequate for detailed study of specific congenital cardiac lesions in young children or infants

The image amplifier employed with combined cardiac catheterization and selective angiocardiography, is capable of demonstrating the pulmonary venous return the left heart and aorta the coronary circulation pulmonic valvular and infundibular stenosis *patent foramen ovale ventricular septal* defect truncus arteriosus the presence and degree of dextroposition of the aorta, and anomalies of the aortic arch

Thoracic Aortography Retrograde Aortography

The contrast medium is injected retrograde through the carotid artery or through a catheter introduced through the radial or ulnar artery into the aorta [31-45] The tip of the catheter must be in the middle of the ascending aorta—not lower because of danger to a coronary artery not higher because of danger to the innominate Thoracic aortography has been used mostly in cases of suspected coarctation of the aorta and clinically atypical patent ductus arteriosus but also in suspected aortic hypoplasia aorticopulmonary fistula and truncus arteriosus The

radial or ulnar artery must be sacrificed The procedure is associated with some hazard Thoracic aortography may also be performed by percutaneous insertion of a polyethylene catheter through the brachial artery

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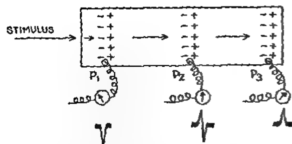


Fig 12 Depolarization of single muscle fiber Impulse starting at S proceeds from left to right P_1 P_2 P_3 are points in surrounding volume conductor and below them are curves registered by galvanometer at those points

muscle fiber is depolarized As depolarization proceeds, the activity front moves from active toward resting muscle and a positive charge (source) precedes while a negative charge follows the path of the impulse or the activity front If an electrode is placed in a conducting medium surrounding the muscle fiber at point P_1 and connected with one pole of a galvanometer while the other pole of the galvanometer is connected to some distant or zero point the galvanometer will register a negative electromotive force since the activity front is moving away from the electrode at P_1 and the electrode at P_1 is therefor facing the negative charge By convention the galvanometer recording device is so arranged that a positive voltage is recorded as an upward deflection and a negative as a downward deflection Hence a negative wave is recorded from the electrode at P_1 On the other hand an electrode in the conducting medium at P_2 would first record a positive deflection as the wave of depolarization approached it and then a negative deflection as the depolarization front passed it An electrode at point P_3 would record only a positive deflection since the wave of depolarization is continually approaching it

With reference to P_2 the instant at which the muscle underlying the electrode is completely depolarized is recorded by the intrinsic deflection [44] The *intrinsic deflection* is a rapid downward deflection from the peak of maximum positivity The greatest positive potential is recorded just as the activation front is about to reach the electrode There is then a sudden fall of potential to zero when the center of the activation front is at the electrode and a rapid increase in negative potential as the activation front passes just distal to the electrode If the electrode is at the last point to be depolarized the downward deflection reaches zero, i e the iso electric line, but does not become negative When the electrode is not directly on the surface of the muscle fiber but somewhat removed in the conducting medium, as for example when electrodes are placed on the body surface rather than on the contracting myocardium, there is a similar but somewhat slower fall from maximal positive to zero or to maximal negative potential, and a somewhat less steep downward deflection is recorded since the activation front is some distance beneath the recording electrode This deflection is termed 'intrinsicoid deflection '[44] However, there is evidence[45] that the *intrinsicoid deflection* in a given area of the heart may not occur at the instant of the sharp downward deflection but somewhat later along the downstroke or even at its nadir This may be related to the vector concept that potential differences on the body s surface are not determined exclusively or even largely by localized potentials (proximity potentials) in the subjacent myocardium i e just below the electrode on the heart s surface, but by the relation of the electrode to the resultant vector of all the electromotive forces generated by the heart

Repolarization

After depolarization has occurred, certain physicochemical processes restore the membrane doublets and the depolarized membrane, cell or fiber is again polarized, with positive charges on the outer and negative charges on the inner side of the surface (Fig 11, *F-I*) During repolarization positive charges face the repolarized areas while negative charges face the areas still depolarized Thus the front of repolarization proceeds with negative charges in advance and positive charges behind

If the depolarized fiber were entirely uniform in its composition and physicochemical properties repolarization would begin first in that region where depolarization had begun and would follow the same path as that of activation If the impulse of depolarization in such a uniform fiber were proceeding toward a point in a surrounding volume conductor where an electrode was connected to a galvanometer a positive wave of depolarization would be recorded since the electrode would be facing the positive charges of the activation front throughout

depolarization If repolarization followed the same course, a negative wave would now be recorded at the same point since the electrode would be continuously facing the negative charges of the repolarization front This alternation of a positive and negative wave is termed a diphasic action current

Repolarization occurs relatively slowly compared with the rapid development of depolarization and the peak potential difference is not as great However the total quantity of electromotive force generated during re-*polarization* (average voltage multiplied by time) is equal to that generated during depolarization The wave of depolarization in a contracting *uniform fiber* is therefore of opposite polarity longer duration and lower voltage than that of the wave of depolarization But the area between the baseline (isoelectric line) and the wave of repolarization is equal to the area of the wave of depolarization

If the muscle fiber is not uniform repolarization may not begin first in the area which was first depolarized and the course of repolarization may not follow the same course as that of depolarization Thus if physicochemical changes occur more rapidly at the right than at the left end of a muscle fiber (e g as a result of cooling the left end) depolarization develops more slowly and persists longer at the left end Accordingly repolarization begins first at the right end where depolarization is first *completed If this muscle fiber is stimulated* at the left end the process of depolarization proceeds from left to right but the front of repolarization begins at the right end (while activation is still present at the left) and proceeds toward the left (Fig 13)

Thus an electrode at the right end of the fiber would be facing positive charges throughout repolarization as well as throughout depolarization The galvanometer records a positive wave during depolarization followed by another positive wave during repolarization This corresponds to the situation in the normal human heart, in which differences in the duration of depolarization in different areas of the ventricles result usually in positive waves representing ventricular repolarization as well as ventricular depolarization The differences in intensity and duration *of activation of different areas of* cardiac muscle are discussed later under the heading 'ventricular gradient' (p 51)

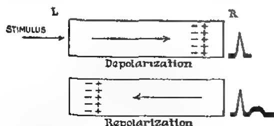


Fig 13 Fiber with slower metabolism and more prolonged depolarization at left end (L) is stimulated at left end Galvanometer at right (R) records a positive wave during depolarization Repolarization begins at right proceeds to left and produces another positive wave

THE LEADS OF THE ELECTROCARDIOGRAM

Cardiac activity is associated with depolarization and repolarization of cardiac muscle and the development of an electrical field in the surrounding tissues The tissues surrounding the heart are considered as a relatively uniform volume conductor for purposes of presenting clinical electrocardiography Electrodes placed on the surface of the trunk or extremities are situated within the electrical field of the heart When these electrodes are connected with the galvanometer in the electrocardiograph machine changes in electrical potential from moment to moment at the sites of these electrodes are recorded as a continuous curve the electrocardiogram, with time as the abscissa and *voltage as the ordinate*

An electrocardiographic *lead* or *derivation* refers to a pair of electrodes on the body s surface between which there is a potential difference and from which the current is led to the electrocardiograph The term ' lead ' is applied also to the electrocardiogram thus obtained from a given pair of electrodes When both electrodes are at approximately equal distances from the heart the lead is called a bipolar lead A so called ' unipolar lead denotes that one of the two electrodes is relatively distant from the heart In clinical practice 12 leads are usually recorded routinely the three standard (bipolar) limb leads, three unipolar limb leads and six unipolar precordial leads Selectors on the electrocardiograph, chosen by means of a switch adjust the proper lead arrangements after all the electrodes are properly placed on the extremities and the precordium and suitably connected to the electrocardiograph

The Standard Leads

The standard limb leads are bipolar leads. Lead I is taken between electrodes placed on the right and left forearms (conventionally referred to as arm); lead II is between the right arm and left leg; lead III is between the left arm and left leg. The polarity of the electrocardiograph's galvanometer is so arranged that an upright wave is recorded in lead I when the left arm electrode is positive relative to the right arm electrode; an upright wave appears in lead II when the left leg electrode is positive relative to that on the right arm; an upright wave occurs in lead III when the left leg electrode is positive relative to that of the left arm.

The Einthoven Triangle and The Einthoven Law (Equation)

Einthoven conceived of the human torso as a sphere at the center of which was an electric current dipole representing the heart's electrical activity. The right shoulder, left shoulder and left hip were regarded as forming an equilateral triangle (the Einthoven triangle) whose apices are on the surface of the sphere; the plane of the triangle was assumed to be parallel to the frontal plane and to contain the dipole at its center. The limb lead electrodes are regarded as being situated at the apices of the triangle, but for practical reasons they are actually placed on the right and left forearms and left leg, which are linear extensions of the shoulders and left hip.

The *Einthoven triangle hypothesis*[1] also assumes that the tissues surrounding the heart form a uniform volume conductor and therefore conduct the electrical impulse uniformly *to the body surface, and further* that the sites of the limb electrodes, represented by the apices of the Einthoven triangle, are relatively distant from the heart and each other and that the heart may be represented as a point source of electromotive forces denoted by the center of the equilateral triangle.

None of these assumptions is exactly correct since the heart is somewhat eccentrically placed in the torso[illegible, 25]; the triangle formed is not equilateral; the heart is not equidistant from the apices, the tissues are not uniform with respect to their conductivity[7] and the size of the heart is relatively large compared to the distance of the electrodes from the heart. However, the assumptions approximate the facts sufficiently to have made the Einthoven hypothesis extremely useful in our understanding of the findings in the electrocardiogram of the human heart.[illegible] The Einthoven hypothesis is the basis also for the concept of the mean electrical axis and the determination of the manifest electromotive forces of the heart, which are discussed later under vectorcardiography (p. 3?).

Since the standard leads are bipolar leads they reveal differences of potential at two sites but do not actually disclose the potential at any single extremity. The lead potential difference in microvolts at any instant is as follows:

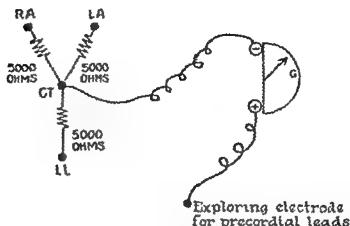
Lead I = Left Arm minus Right Arm
Lead II = Left Leg minus Right Arm
Lead III = Left Leg minus Left Arm

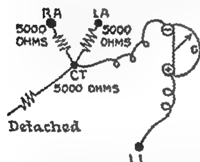
It is apparent from these equations that if electrocardiograms were taken simultaneously with the three leads at any given instant the potential in lead II is equal to the sum of the potentials of leads I and III (Einthoven's Law or Equation).[2] When the leads are recorded in succession as they are usually, this relationship is only approximately correct, but may be used as a check on the accuracy of the application of the electrodes.

Unipolar Leads and Wilson's Central Terminal

Unipolar leads are designed to disclose the potential at a given site relative to some distant or zero point in the electrical field of the heart. One electrode placed relatively close to the heart is termed the exploring electrode, while the other placed at a relatively distant site is termed the indifferent electrode. Even so-called unipolar leads are *actually bipolar in that two wires running to* different electrodes are required to complete the electrical circuit to the galvanometer. However, while one wire leads to the exploring electrode on an extremity or chest wall, the other wire leads to an indifferent electrode with negligible potential. But no matter how distant from the heart is the location of the indifferent electrode on the body surface, its potential is not negligible, hence various methods have been suggested to obtain such an electrode with zero or negligible potential.

The method of Wilson employs a *central terminal* representing an approximate "zero potential."[illegible] The central terminal is connected on the one side with the negative pole of the electrocardiograph galvanometer and on the other with each of the three extremi





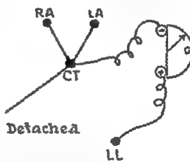


Fig 14 Connections for Wilson's Central Terminal for precordial leads Wilson's Central Terminal for unipolar limb leads and Goldberger's Central Terminal for unipolar limb leads CT central terminal G galvanometer RA right arm LA left arm LL left leg (foot)

ties the right and left arms and the left leg with a resistance of 5000 ohms interposed between each of these extremities and the central terminal (Fig 14) The positive pole of the electrocardiograph galvanometer is connected by another wire to the exploring electrode and a positive potential at the exploring electrode is recorded as an upright wave

The potential at the central terminal is the average of the potentials at these extremities If the assumptions on which the Einthoven triangle hypothesis is based are valid the potential at the central terminal is virtually zero since the sum of the potentials at the three apices representing the site of the limb electrodes at a given instant is equal to zero (Einthoven equation) Furthermore the central terminal potential does not fluctuate from moment to moment during electrical activation and repolarization of the heart if the approximate validity of the Einthoven hypothesis is accepted Actual measurements by experimental methods are in essential support of these concepts[18] although they have been variously criticized[3, 57, 58, 10] The accuracy of the assumption that the central terminal is at zero potential depends not only on the validity of the Einthoven equilateral triangle hypothesis but also on the identical values of the skin resistance under the three extremity electrodes Differences in skin resistance are difficult to avoid in practice but may be minimized by carefully scrubbing the patient's skin before applying the electrodes and by the introduction of the fixed resistors Various experimental studies including the use of torso models filled with a

homogeneous conductor in which is immersed a current dipole eccentrically placed, indicate that the Wilson central terminal voltage departs from the ideal zero value by approximately 15 to 40 per cent of the maximum value of the manifest heart vector [21]

Unipolar Precordial or Chest Leads

To obtain unipolar leads from the chest wall, the exploring electrode connected with the positive pole of the electrocardiograph galvanometer is placed successively on various sites of the precordium while the negative pole is connected to the Wilson central terminal (p 22) Unipolar leads from either the chest or limbs are labeled V leads followed by a symbol denoting the site of the electrode The usual unipolar precordial leads are taken from the following sites [2]

- V_1—Fourth intercostal space immediately to the right of the sternum
- V_2—Fourth intercostal space immediately to the left of sternum
- V_3—Midway between V_2 and V_4
- V_4—Fifth intercostal space in midclavicular line
- V_5—Left anterior axillary line at same horizontal level as V_4
- V_6—Left mid axillary line at same horizontal level as V_5

Additional leads are occasionally desirable V_{3R} and V_{4R} are taken with the electrode at positions corresponding to V_3 and V_4, respectively but on the right side of the sternum V_{4R} being particularly useful to reveal right ventricular hypertrophy and conduction disturbances of the heart, the latter especially in children V_7 may be taken at the same horizontal level as V_6 but in the posterior axillary line while V_8 (or V_B) is at the same level in the left scapular line A unipolar chest lead from the xiphoid or ensiform process is designated V_E Leads may also be taken at higher levels e g, in the line of V_4 but in the fourth third or second intercostal space These are designated $V_{4(4)}$, $V_{4(3)}$ or $V_{4(2)}$, respectively or the symbols V'_4, V''_4, or V'''_4 respectively may be used There are also advocates of the use of chest foot leads (CF leads) in which the negative pole is connected with the left leg electrode and the positive pole to the various chest sites (CF_1 CF_2 CF_3 etc) Similarly, chest right arm leads (CR leads) or chest left arm leads (CL leads) may be taken with the negat pole connected to the right or left arm spectively or chest-back leads (CB_1 etc) with the negative pole connected back Special bipolar thoracic leads h employed to explore the cardiac elect in the horizontal plane [15]

Unipolar Limb Leads

The exploring electrode is pl limb under study and is con positive pole of the electrocard the wire from the other pole a central terminal (Fig 14) C fied the central terminal respects He removed the ances since he felt that th influence others have ind introduce additional err the wire from the centr under study since th to the negative ele therefore counter wire which lead po itive pole (I resulting elect per cent great that limb terminal [41] He are call d designated follow mented) follow cerned i e aVR for the left arm, and aVF for the foot) The a' is omitted if the Wilson central terminal is used and the leads are not augmented Actually Wilson employed an augmented limb lead in that he disconnected the central terminal connection to the limb under study, but retained the 5000 ohm resistances (Fig 14) The central terminal is no longer at zero potential when one of the extremity wires is detached as in the augmented leads The original central terminal of Wilson with virtual zero potential is still retained for precordial unipolar leads In actual practice electrodes are attached to the four limbs and to the various precordial sites, while the proper leads are obtained by merely turning the switch in a lead selector which is incorporated in the electrocardiograph

Esophageal Leads[26, 6, 33]

An esophageal electrode which is a small German silver pellet is attached to a plastic tube or duodenal catheter, and is connected

by insulated copper wire to the left arm lead and thence to the positive electrocardiograph pole. The other pole of the electrocardiograph attached to the right arm lead is connected with the central terminal of Wilson and the electrocardiograph is set at lead I. The tube or catheter is passed into the stomach and electrocardiograms are recorded from successive esophageal levels as the tube is withdrawn gradually from the subdiaphragmatic to the supracardiac level. The site of the electrode is determined from measurements marked on the tube and by the presence of an intrinsic deflection of the P wave as long as the tube is contiguous to the atrium. Esophageal electrocardiograms record atrial, transitional or ventricular deflections according to the position of the electrode. The first group is recorded when the electrode is 32.5 to 47.5 cm. from the anterior nares, the second between 40 and 50 cm. from the nares, and the third from 42.5 to 52.5 cm. or more from the nares. Because of the inaccuracies in estimating the electrode's position by the distance from the nares, Scherlis et al.[8] determined its position by fluoroscopic control. They employed a rubber tube with fifteen electrode rings of German silver 1.75 cm. apart, each with its thin wire connection for electrocardiographic attachment. Esophageal leads are designated by the symbol E followed by a numerical subscript denoting the distance in centimeters from the mouth or external nares to the esophageal electrode, e.g., E_{46}. Esophageal leads may be useful in the diagnosis of atrial enlargement, arrhythmias and infarction of the posterior wall of the left ventricle.

Intracardiac electrocardiograms, regarded as direct leads from the endocardial surface of the heart, have been obtained by cardiac catheterization, a small German silver electrode attached to the catheter serving as the exploring electrode.[31, 35, 38] The site of the catheter electrode is determined by fluoroscopy, pressure recordings and oximetry. The usefulness of intracardiac electrocardiography has been chiefly limited to research, especially with respect to our understanding of the genesis of the electrocardiogram.

Intrabronchial electrocardiograms[40, 8] have likewise been studied, but only for research.

Fetal Electrocardiography[69, 49]

An electrocardiogram of the human fetus in utero may be recorded after the fourth month of pregnancy, but not with regularity until after the sixth month. A preamplifier must be used with the conventional electrocardiograph, or an electroencephalograph may serve to record the electromotive forces generated by the fetal heart. Two abdominal electrodes may be used for a bipolar lead, or Wilson's central terminal may be employed as the indifferent electrode while the exploring electrode is applied successively over various parts of the abdominal wall of the mother. The electrocardiograph is standardized so that 1 millivolt causes a deflection of 10 cm. Fetal electrocardiography may be of value chiefly for the diagnosis or verification of fetal life.

The fetal electrocardiogram is characterized by small monophasic or diphasic deflections normally at the rate of 140–150 per minute, interrupted by maternal complexes. Sinus arrhythmia and premature contractions are not uncommon, and occasional instances of fetal atrial fibrillation and heart block have been reported.[24, ■]

THE NORMAL ELECTROCARDIOGRAM AND ITS GENESIS

The electrocardiogram of the human heart is composed of a series of waves designated in succession by the letters P, Q, R, S, T and U.[8, 83, 46, 87, 17] The horizontal portions of the record (isoelectric line) are called segments, which are designated by the letters of the preceding and following waves, e.g., P-R segment, R-T segment or S-T segment. The distance or time *interval* between the waves is measured in seconds from the beginning of one wave to the beginning of the next. Electrocardiographic paper is marked off by vertical time lines and the paper is fed at such a rate that the interval between two fine vertical lines is 0.04 sec.; every fifth vertical line is darker and marks off 0.2 sec. Horizontal lines above and below the isoelectric or base line are 1 mm. apart and serve to measure the electromotive force or potential difference represented by the various waves. The electrocardiograph is standardized so that the curve is deflected upward by 10 mm. when 1 millivolt is added to the circuit. Consequently, the amplitude of any wave can be measured in millimeters or millivolts, 10 mm. representing one millivolt. For facilitating measurements every fifth horizontal line on the electrocardiograph paper is wider and

darker and the distance between two such lines is 5 mm or 0 5 millivolt

The P Wave

The P wave represents the spread of the impulse (depolarization or wave of accession) from the sinoatrial node tangentially along the atrial walls, and to the atrioventricular node, at the approximate rate of 500 mm per sec [ ] The right atrium is activated 01 sec before the left A positive charge (source) precedes this activation wave or band of dipoles while a negative charge (sink) remains behind in the activated muscle A difference of 50 to 100 millivolts may exist between polarized and depolarized adjacent fibers The amplitude and polarity of the P wave depend in part on the direction and magnitude of the depolarization wave but also on the position of the electrodes on the body's surface (points in the heart's electrical field) from which the electrocardiographic leads are taken As *indicated above a positive or upright wave* will be inscribed when the electrode is facing the positive pole of the doublet i e, the on coming accession wave, and a negative or inverted wave when the electrode is so placed that it faces the negative charge i e when the accession wave is moving away from the electrode

The amplitude of the P wave is determined in part by the strength of the electromotive charges developing in the atrial muscle But for any given heart the amplitude of the P wave will be larger the more nearly the lead line from the activated atrium to the electrode parallels the direction of the mean electrical axis of atrial depolarization The *mean electrical axis* refers to the average direction of the electromotive forces generated during depolarization (or during repolarization) There is no P wave or P may be termed iso electric when the lead line is perpendicular to the mean electrical axis of atrial depolarization The first portion of the P wave represents chiefly right atrial, and the latter portion of the P chiefly left atrial activation [58]

The P waves are usually upright in leads aVL and aVF since the electrodes on these extremities face the positive charges of the oncoming depolarization wave whereas P in aVR is negative since the wave is moving away from the electrode on the right arm The greatest amplitude of P is usually in aVF since this lead is most nearly parallel to the mean electrical axis Corresponding to these findings the P wave is usually upright in leads I and II but may be upright, diphasic isoelectric or inverted in lead III since the P in these leads is the difference between the P waves in two of the unipolar limb leads The P wave may be negative but is usually diphasic and of low voltage in V_1 and sometimes in V_2, since it is initially positive as the right atrial activation wave approaches the electrode and later negative as the activation wave moves away from the electrode to activate the left atrium A P wave is abnormally high if it exceeds 3 mm in the bipolar extremity leads or 2 5 mm in the precordial or augmented unipolar limb leads, and abnormally broad if its duration exceeds 0 10 sec Normally the height of the P wave varies between 0 5 mm and 2 5 mm but is less than 2 mm in leads I and III [31] [ ] An increase in amplitude or width of the P wave is usually associated with atrial hypertrophy or dila *tation[73] as is observed notably in cases of* mitral stenosis atrial septal defect tetralogy of Fallot and cor pulmonale

Repolarization of the atria is represented by an atrial T wave (T_P or T) following the P wave and opposite in direction to the P wave The atrial T wave is usually invisible in conventional electrocardiograms either because of low amplitude or because it is concealed within the QRS complex It may occur after the R wave and cause a slight depression of the S T segment

The P Q or P R Interval

The P-Q or P R interval is measured from the beginning of the P wave to the beginning of the Q wave or to the beginning of the R if no Q wave is present The P Q segment from the end of P to the onset of Q represents the delay in transmission of the impulse from atria to ventricles in the bundle of His but chiefly in the atrioventricular node The atrial T wave (T_P) is usually hidden in this segment but may be visible if the P R interval is prolonged In adults with cardiac rates between 60 and 80 per minute the P R interval ranges between 0 12 and 0 20 second,[60] although occasionally rates up to 0 22 may be noted in apparently normal hearts [ ] [ ] [54] When the P R interval appears prolonged the measurement should be checked by subtracting the longest QRS interval in standard leads from the longest P S interval in these leads With more rapid cardiac rates of 100–120 per minute, 0 18 or 0 19 is the upper limit of normal

This relationship between the P-R interval and cardiac rate has been questioned.[60, 61] The P-R interval tends to increase with age, the upper limit of normal being 0.16 in children,[1] 0.18 in adolescents and 0.2 second in adults.[87, illegible] The P-R interval is abnormally short if it is 0.1 second or less. This is observed in the Wolff-Parkinson-White syndrome (p. 106) and nodal rhythm (p. 328).

The QRS Complex

The QRS complex, also termed the initial ventricular deflection, represents depolarization of the ventricle. The Q wave is the first negative deflection and the R wave the first positive deflection of the complex. A downward deflection following the R wave is termed an S wave. A second upward deflection after an S wave is called R' and a second downward deflection S'. If the entire complex consists of only one downward deflection, it is termed a QS wave. Capital or lower case letters are used to indicate large or small waves respectively, a small wave being defined as one which does not exceed half the amplitude of the tallest wave of the QRS. The Q wave or R wave or both may be absent.

A *Q wave* may occur normally in any lead. When it is present in lead I, it occurs also in precordial leads to the left of the interventricular septum. Its mean depth is usually less than 0.5 mm. in standard leads in adults with a maximum depth of 2 mm. in lead I and 3 mm. in leads II and III.[17, illegible, 73] In children and infants the Q wave is normally deeper.[70, 87] In aVR in adults the mean value of Q is about 2.5 mm. A Q wave is regarded as prolonged if its duration is 0.04 second or more except when QS forms the entire initial ventricular complex.[5]

The *duration of the QRS waves*, measured in the limb lead with the widest QRS from the beginning of the Q to the end of the last wave of the complex, usually ranges between 0.06 and 0.08 second, and does not exceed [illegible].10 second normally. Occasionally a QRS interval of 0.11 second or even 0.12 second may occur in a subject with an apparently normal heart. The QRS interval is usually shorter in children (0.04 to 0.08 below the age of 5, and 0.05 to 0.09 between 5 and 14); the QRS interval also diminishes slightly with increasing cardiac rate.[61]

The amplitude of the tallest wave of the QRS complex should measure 6 mm. (0.[illegible] millivolt) or more in at least one of the standard limb leads. The tallest R wave is usually between 5 and 15 mm. in amplitude, with maximal values up to 28 mm. in the standard leads in normal adults.[illegible, 73, 67, 4, 17, illegible] In the precordial leads, the mean height of the R wave ranges between 3 mm. and 14 mm., the tallest usually in V_4 or V_5 and the lowest in V_1. The voltage of the QRS is regarded as high if the highest QRS deflection exceeds 25 mm. (2.5 microvolts) in the bipolar extremity leads, 20 mm. in the augmented unipolar limb leads or 50 mm. in any of the conventional precordial leads.[67, 4, 17, 87] Low voltage of the QRS denotes that the highest deflection is less than 5 mm. in the limb leads and less than 10 mm. in the precordial leads.

The QRS in Limb Leads. The normal electrocardiographic pattern of the QRS complex in the unipolar and standard limb leads varies with the electrical axis of the heart. Usually in aVR there is an rS or Qr pattern, rarely an RSR' or QS pattern with unusual position of the heart. T is normally inverted.

When aVL faces the epicardial surface of the left ventricle, it shows a qR or qRs pattern and T is usually upright. When it faces the epicardial surface of the right ventricle, as it does in a vertical or clockwise rotated heart, it shows an rS, RS or QS pattern, T is usually upward but may be inverted. The more nearly parallel the lead is to the electrical axis, the taller the main positive deflection if it faces the left ventricle, the deeper the main negative deflection if it faces the epicardium of the right ventricle. In a similar manner, lead aVF is more likely to face the left ventricular epicardium and show a qR or qRs pattern, the more vertical or clockwise rotated is the electrical axis of the heart, and it is more likely to face the right ventricular epicardium and show an rS or RS pattern, the more nearly transverse or counterclockwise is the electrical axis of the heart.

The standard limb leads show patterns which are the summations of the findings in the corresponding unipolar limb leads. The major deflections are upright in all three standard leads in hearts which tend to be vertical, but S_1 (the S wave in lead I) tends to become deeper than R_1 and R_3 taller than R_1 the more nearly vertical is the heart. In the normal heart tending toward the transverse position, there is apt to be a Q wave but no S wave in lead I, R_1 tends to be taller

than R_3, and there is a deep S wave in lead III and sometimes in lead II There may be a W shaped QRS of low voltage in lead III T is upright, but may be inverted in lead III especially as the heart tends to be transverse

Time of Intrinsicoid Deflection (QR Interval) The interval from the onset of the QRS complex to the peak of the R wave (intrinsicoid deflection) is usually about 0 02 second with a maximum of 0 03 second in right precordial leads (V_1 and V_2) while in left precordial leads it is usually about 0 03 to 0 04 second with a maximum of 0 05 second[67] The longer interval in leads overlying the left ventricle is presumably due to the longer period required for the impulse to traverse the greater thickness of the left ventricle If two peaks are present RR' the one with the largest downstroke is considered to be the characteristic intrinsicoid deflection

QRS Complex in Precordial Leads[76, 80, 81, 67, 4, 86, 87] The findings in precordial leads suggest that local underlying myocardial areas strongly influence the electrocardiogram because of the profound alterations that may occur with relatively small changes in the site of electrode placement but vectorcardiographic theory regards the former alterations as resulting from changes in the summation vector determined by total cardiac activity from moment to moment (p 33) Leads V_{3R} V_E V_1 and V_2 are termed right precordial leads facing the epicardial surface of the right ventricle There is a small r and a deeper S in V_1 and V_2 but no Q The R wave increases progressively in amplitude in leads further to the left

When the R wave is equal in amplitude to the S wave the so-called transition between right and left ventricular potential has been reached, usually in V_3 or V_4 At this point the lead is perpendicular to the mean electrical axis From V_4 to V_6 there is usually a gradual rise in the height of the R wave and a fall in the S wave with disappearance of the S in V_5 or V_6 A Q wave is often present in V_5 and/or V_6 Occasionally with rotation of the heart positive left ventricular potentials are not dominant until V_7 or V_8 and, conversely the potentials usually associated with right precordial leads may be found only when the electrode is far to the right as at V_{3R}

A Q wave is ordinarily absent in V_1 to V_3 but often appears as a small wave in V_5 or V_6 The Q wave is due to septal activation and appears in leads from the left side of the heart since the septum is initially activated from left to right i e the activation front moves away from the left precordial electrodes[88]

V_1 may disclose a small R wave if septal activation proceeds toward the electrode, or R may be absent if septal activation proceeds perpendicularly to the lead line from the electrode S is present and relatively large Normally R in V_1 does not exceed 7 mm (0 7 mv) and averages 3 5 to 5 mm while S averages between 10 to 12 mm The R/S ratio is less than 1 T may be inverted, isoelectric or upright

V_2 usually possesses an R wave larger than R in V_1 if present, since it is in more direct line with the septal activation wave There is an S wave which is deeper than that in V_1 if the heart is rotated counterclockwise smaller if the heart is rotated clockwise The T wave is upright in leads V_2 to V_6 in adults whereas in children and some young adults T may be inverted normally in V_1 to V_4

V_3 shows progressive increase in the height of R unless there is an anteroseptal infarct left ventricular hypertrophy or left bundle branch block The S wave decreases R is larger than S in vertical hearts smaller than S in horizontal hearts

V_4 reveals that R has become taller than S especially if the apex is relatively anterior S does not disappear until the electrode is over the last portion of the ventricle to be activated, i e , in leads further to the left

V_5 and V_6 show a large R which may occasionally be smaller than R in V_4 S is usually absent

Genesis of the QRS Complex[76, 80] The theories invoked above to explain depolarization of a cell (p 18) or of a single muscle fiber (p 19) may be applied also to an exposition of the genesis of the QRS complex associated with activation of the ventricles The heart may be regarded as analogous to a polarized cell The ventricles are perceived as an irregular U shaped shell formed by the free walls of the ventricles partitioned by the interventricular septum and open at the base in the region of the valves (Fig 15)

The cardiac impulse or excitation wave, initiated normally in the sinoatrial node having traversed the atria, the atrioventricular node and bundle of His spreads through the right and left bundle branches and the ramifications of the Purkinje network

of the conduction system in the subendocardial regions of the two ventricles almost simultaneously. The excitation wave then traverses the ventricular muscle perpendicularly from endocardial to epicardial surface, much less rapidly (approximately 400 mm. per second) than it spreads through the septum and Purkinje fibers (approximately 4000 mm. per second). Recent studies of the spread of activation in the left ventricular wall of the dog[64, 84, 19] indicate that the inner third is activated more or less synchronously, the impulse traveling at the rate of 2000 mm. per second or more; needle electrodes in the inner third of the ventricle yield QS complexes identical with those from the cavity, whereas RS complexes arise in the outer portion of the ventricle. The muscle

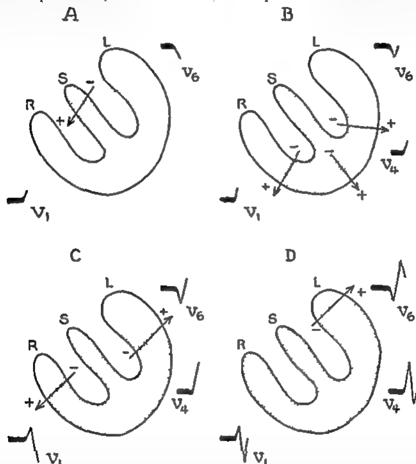


Fig. 15. Ventricular depolarization. Diagram of heart and electrical field in horizontal plane. R, Free wall of right ventricle; L, of left ventricle; S, septum. Stippled area, activated muscle (negative). Arrows indicate direction of activation wave. A, B, C, D, Successive stages in ventricular depolarization.

A, Onset ventricular depolarization. Septum depolarized from left to right. Positive upward deflection in right precordial lead (V_1) toward which activation wave is directed. Downward deflection in left precordial lead (V_6).

B, Septum, apex of left ventricle, part of free wall of right ventricle depolarized. Activation of right ventricle toward right continues positive wave in right precordial lead. Beginning activation of left ventricle may give small positive deflection in V_4, but activation wave is still directed away from or perpendicular to V_6. Therefore no upright deflection in V_6.

C, Septum and right ventricle depolarized. Left ventricle largely depolarized with activation wave of maximal cross-sectional area directed to the left. Maximal upright (R) wave in V_4, somewhat less in V_6. Negative deflection in right precordial lead V_1 as stronger electromotive forces of left ventricle overbalance right ventricular electromotive forces.

D, Depolarization completed in septum and right ventricle. Last phase of depolarization of basal portion of lateral wall of left ventricle. Activation wave directed to left but cross-sectional area diminished. At V_4 negative (S) wave as activation wave moves away from overlying electrode. At V_6 no S wave as depolarization will finish in this area. At V_1, V_4, V_6, R and S return to isoelectric line as cross section of activation wave diminishes.

mass of the left ventricle, being larger and thicker than the right develops greater electromotive forces and requires more time for depolarization than the right ventricle

The direction and magnitude of the electrical axis are continually changing from instant to instant as the process of ventricular depolarization progresses The appearance of the QRS complex in terms of direction and magnitude of the individual waves is determined by these changes in direction and magnitude of the activation wave (i e, its electrical axis) and by their relation to the site of the electrode from which the electrocardiogram is registering potential differences The major deflection of the QRS will be upright (positive polarity) when the activation wave is moving toward the recording electrode, downward (negative polarity) when the activation wave is moving away from the recording electrode

In the initial phase of depolarization the wave of activation traverses the interventricular septum from the left to the right side (Fig 15*A*) An electrode on the right side of the precordium (lead V_1) will record an upright wave since it faces the positive charge of the approaching activation wave An electrode on the left side of the precordium (leads V_5 and V_6) records a small negative wave the Q wave, because the septal activation wave from right to left is moving away from these electrodes Electrodes which are intermediate in position may record no wave at this moment since the lead lines from these electrodes to the activation wave are perpendicular to the electrical axis of the activation wave

With the spread of the impulse the entire septum, *the apex and much of the free wall of* the right ventricle are activated (Fig 15*B*) The electrical axis is still directed to the right and the right precordial leads (V_1) record a positive wave Its amplitude depends on the degree to which the positive electromotive forces directed toward the right electrodes overbalance the negative electromotive forces from the activated apical portion of the left ventricle which are directed away from V_1 The early activation of the left ventricle now produces electromotive forces directed to the left and records the onset of an upright (R) wave in left precordial leads

As activation of the right ventricle is being completed and the free wall of the left ventricle becomes almost completely depolarized (Fig 15*C*), the predominant electromotive forces and therefore the electrical axis are directed to the left Therefore leads from electrodes on the right arm (aVR) and right precordial leads (V_1 and V_2) show a downward deflection (S) since the predominant left ventricular accession wave is moving away from these electrodes as it proceeds from the subendocardial toward the epicardial area of the left ventricle At the same time this activation wave is directed *toward* left precordial electrodes and toward an electrode on the left arm, and a positive or R wave is recorded in leads V_4 to V_6 and in aVL

With complete depolarization of the septum and right ventricle a small portion of the base of the left ventricle remains to be depolarized Activation of this final portion of the left ventricle is associated with electromotive forces from right to left which are directed toward left precordial and left arm leads The activation wave in this last portion of the left ventricle to be depolarized which is recording a *positive (R) wave in V_5 and V_6 may be* moving away from V_4 and therefore recording a negative (S) wave in V_4 No S wave is usually observed in leads from the basal portion of the lateral wall of the left ventricle since this is the last area to be activated and the activation wave does not proceed away from it

It should be noted that this concept of cardiac depolarization (and likewise of repolarizaton) in terms of the dipole wave or band theory is not generally accepted by those who regard *the electrocardiographic* representation of cardiac excitation and recovery as the summation of two somewhat *asynchronous monophasic action potentials* ("interference theory") [18]

The RS T Segment

The S T, R T, or RS-T segment is the segment between the end of the QRS complex and the onset of the T wave It is measured from the end of the S to the beginning of the T wave or from the end of the R if no S wave is present The point marking the end of the QRS is termed the S-T junction or J The RS T segment represents a state of unchanging polarization between the end of depolarization and the beginning of repolarization, or a stage at which terminal depolarization occurs simultaneously with, and is neutralized by, commencing repolarization Electrodes in any part of the heart s electrical field face an equal number of positive and

negative charges and the galvanometer records no electromotive force The RS-T segment of the electrocardiogram is therefore usually isoelectric and lies flat along the base line, but slight elevations are normal and not uncommon

The S-T segment is displaced or deviated from the baseline whenever complete depolarization is delayed and an increase in repolarization has occurred before depolarization is completed in one or both ventricles To determine RS-T displacement the level of the S-T segment is compared with that of the following T-P segment and not with the preceding P-R segment[8] This will prevent an erroneous diagnosis of S-T deviation when the S-T segment is compared with a P-R level which is deviated by a T_P (atrial T) wave An elevation or depression of less than 1 mm in the standard leads is generally regarded as within normal limits Since the normal tendency is for the RS-T segment to be isoelectric or slightly elevated in precordial leads a depression of even 0.5 mm may be abnormal while a similar degree of elevation is not Accurate measurement of an elevation or depression of the S-T segment requires that the baseline or isoelectric level should not be drifting from the horizontal

The duration of the S-T segment increases with slowing of the heart rate and varies from 0 10 second when the rate is 100 per minute to 0 15 second at a rate of 50 per minute The S-T segment is slightly longer in women than in men or children In precordial leads the S-T segment is usually very short or absent because of earlier recording of repolarization in these leads The repolarization which begins in small areas before completion of depolarization is not as apt to be recorded in the more distant unipolar limb or standard leads The S-T segment in precordial leads may be depressed normally as much as 1 mm but more frequently it is elevated to as much as 2 mm or more above the isoelectric level When T is tall there is more apt to be an elevation of the RS-T segment but this elevation does not exceed one quarter the height of the T wave

Abnormal RS-T deviation (elevation or depression) may occur in a variety of conditions but notably with acute myocardial infarction subendocardial ischemia or infarction, acute pericarditis digitalis drug ventricular hypertrophy, ventricular aneurysm tachycardia, hypopotassemia and other electrolyte disturbances

The T Wave

This wave represents ventricular repolarization and occurs during the latter part of systole It is normally upright in leads I and II upright or inverted in lead III Its height averages 3 mm in lead II, 2 mm in lead I and 1 mm in lead III In precordial leads the T wave usually ranges between 3 and 8 mm in height, being somewhat taller in men than in women High voltage of the T wave denotes that its height exceeds 7 mm (0 7 millivolt) in any bipolar extremity lead, 5 mm in any augmented unipolar limb lead or 20 mm in any precordial lead[17] Low voltage of the T wave is indicated when the highest T wave is less than 1 mm in all the extremity leads and less than 2 mm in all the usually recorded precordial leads In lead I a T wave which is less than 0 5 mm in height or a negative T wave is abnormal A negative T wave in lead II in the supine subject is usually abnormal but T is often inverted normally in lead III, especially in obese patients and those with a transversely placed heart T is usually inverted in aVR, usually positive up to 4 mm in aVL but occasionally inverted 1 to 2 mm, usually upright up to 5 mm in aVF but occasionally negative by 1 mm In children the T wave is almost always upright in aVL and aVF The T wave is usually upright in the precordial leads in the adult occasionally inverted in V_1 and less frequently in V_2 to V_4 The T wave is almost always inverted in V_1 and V_2 and often in V_3 in infants and is usually inverted in right precordial leads (V_1) in children and some young adults[73] [illegible] Wasserburger[74] encountered frank inversion of the T waves in the right and midprecordial leads in 10 [illegible] per cent of 131 adult Negro males Because of the resemblance to the negative T waves in infants and young children he termed it the juvenile pattern' and cautioned against interpreting it as evidence of myocardial disease Similar changes could be induced by hyperventilation and abolished by vagal blocking agent [illegible]

A T wave may be inverted in adults in leads I or II or in precordial leads as a result of smoking drinking cold water severe emotional upsets, digitalis drugs insulin, hypopotassemia and hypocalcemia beriberi, hyperthyroidism and myxedema, and as the result of hyperventilation[75] The T wave is inverted

in lead I, aVL and left precordial leads in connection with left ventricular hypertrophy and in leads II and III and often in right precordial leads in right ventricular hypertrophy. Inverted T waves in leads I, II or III or in unipolar or precordial leads may be due to myocardial disease, especially myocardial infarction, coronary insufficiency of varied etiology and in bundle branch block.

It was previously mentioned that in a uniform muscle strip one would anticipate that the wave of repolarization (T wave) would be directed opposite to that of depolarization (QRS), since repolarization should begin in the same region as depolarization and follow the same course. If such uniformity applied to human heart muscle, there would normally be a negative T wave when the QRS was predominantly positive. However, possibly because of a slower rate of metabolism and therefore delayed completion of depolarization in the subendocardial region, repolarization begins in the subepicardial portion of the myocardium and proceeds toward the subendocardium, in opposite direction to depolarization. As a result of this lack of ventricular uniformity and consequent differences in intensity and duration of depolarization in different ventricular areas (ventricular gradient, p. 51), the T wave is in the same direction as the major deflection of the QRS.

The Q-T Interval

The Q-T interval represents the duration of ventricular electrical systole including depolarization and repolarization. It is measured from the beginning of the QRS to the end of the T wave, preferably in the lead showing the tallest and most distinct T wave termination. Accurate measurement is often impossible when the T wave is low, when the U wave is well developed, when the end of the former and beginning of the latter are indistinct, and when P and T are superimposed.[71, 45] Accurate measurement is also difficult or impossible in the presence of bundle branch block or ventricular arrhythmias. Accuracy may be increased by taking the average duration of several or many Q-T intervals. The Q-T interval is most accurate in the lead in which it is most clearly demarcated and usually in which it is longest. The Q-T interval varies with the heart rate, increasing as the latter slows. The Q-T interval is somewhat shorter for men and children than for women.

The normal Q-T interval for a given cardiac rate may be calculated from Bazett's formula.[9] Normal Q-T = $K\sqrt{R\text{-}R}$, in which K is a constant equal to .37 for men and children and .40 for women and R-R represents the interval between two R waves. The ratio between the measured Q-T interval and this calculated normal Q-T interval is sometimes termed the Q-T ratio. A corrected Q-T interval, QT_c, has been employed by Taran and Szilagyi,[71] $QT_c = \frac{\text{Q-T (as measured)}}{\sqrt{R\text{-}R}}$. The upper limit of normal of the QT_c is said to be 0.405. However, a variety of other formulae have been promulgated to determine the normal Q-T interval and the values obtained differ significantly, especially when the cardiac rate is somewhat above or below the most common normal range.[11, 4, 1] Values between 0.425 and 0.445 have been given as the upper limit of normal. In view of the difficulties in measuring the Q-T interval and disagreement as to its normal range, one should be cautious in utilizing it as a diagnostic sign.

The Q-T interval may appear prolonged because of increased duration of the QRS, of the S-T segment or of the T wave or because of erroneous inclusion of the U wave. The adjusted Q-T interval is the measured Q-T less the duration by which the QRS is prolonged. It indicates whether there is an abnormality in the Q-T interval due to repolarization.

A prolonged Q-T interval occurs in hypocalcemia, in uremia probably because of hypocalcemia, and in hypokalemia. In hypocalcemia the prolongation appears to concern chiefly the S-T segment, in hypokalemia the T wave duration. In hypokalemia the apparent prolongation may be due to the presence of a distinct U wave which may be difficult to differentiate from the T. Similarly, prolongation of the Q-T interval, which may occur after quinidine or atabrine, or after a cerebrovascular accident,[9] may also be due to the presence of a *U* wave. Less marked prolongation of the Q-T interval may be associated with rheumatic and other myocardial disease, myocarditis, pericarditis, pulmonary embolism, beriberi and myxedema.

The Q-T interval may be shortened after digitalis drugs, in hypercalcemia and hyper

kalemia (conditions causing subendocardial anoxia and a diminished ventricular gradient) and by increased vagal tone (adolescence)

The U Wave

The U wave is a low broad wave usually not exceeding 0.5 mm in height in standard leads. It is present in the standard leads in the majority of subjects. It occurs 0.02 to 0.04 second after the T wave and its duration is about 0.2 second.[55]

A prominent or widened U wave occurs with hypokalemia, with quinidine, digitalis and epinephrine administration and in a variety of conditions. A negative U has been observed with variable frequency in cases of hypertension and left ventricular hypertrophy and occasionally with myocardial infarction.

The origin of the U wave is unknown. It has been interpreted as corresponding with the after potential in nerve since the U wave occurs coincident with the supernormal phase of ventricular excitability. It has also been attributed to the mechanical effect of ventricular distention during the early phase of rapid filling.

VECTORCARDIOGRAPHY (VECTOR ELECTROCARDIOGRAPHY)

Relationship Between Electrocardiography and Vectorcardiography

The electrocardiogram records the electromotive forces generated by the heart from moment to moment as projected onto various sites of the body's surface. The electrocardiogram is a scalar delineation of these forces since it represents only the magnitude (voltage) and sense (positivity or negativity) but not the direction of these forces. On the other hand, a vector is an entity possessing not only magnitude and sense but also direction. A vector is generally represented by a straight line in the form of an arrow, its length denoting magnitude, the arrow head pointing its direction, and the position of the arrow with respect to some axis of reference indicating positivity and negativity.

The electromotive forces generated by the heart from instant to instant may be recorded as vectors.[111] These instantaneous vectors of the electrical activity of the heart may be represented on some coordinate axial system by a successive series of arrows whose origin is at the same zero point in the axial system but whose direction, magnitude and sense may change from moment to moment in the course of a single cardiac cycle. A curve joining the terminus or arrowhead of these vectors forms a loop which is known as a *vectorcardiogram*.

The vectorcardiogram is merely a different form of representation of the same cardiac electromotive forces as are depicted by the electrocardiogram. In the electrocardiogram these electromotive forces are delineated as a scalar function of time; in the vectorcardiogram, as a vector function of time. The electrocardiogram records the potential difference (voltage) from instant to instant at a given *point* on the body surface relative to some other *point*; each record represents a *single lead*. The conventional vectorcardiogram records the projection of the heart's electromotive forces on a *plane* of the body surface; each record represents the resultant of two or more leads in that plane. The electrocardiographic leads in any plane can be determined from the vectorcardiogram projected on that plane; conversely, the plane vectorcardiogram can be determined and in practice is actually determined from two leads in that plane. Neither is subservient to the other. As indicated, both the vectorcardiogram and the electrocardiogram are graphic records of the projections on a plane or on a line, respectively, of the same electromotive forces. On the other hand, even when electrocardiographic leads are recorded simultaneously and from the same electrode sites as the vectorcardiogram, neither the electrocardiogram nor the planar vectorcardiogram constructed manually from any two electrocardiographic leads provides as much information as the vectorcardiogram taken from the same electrode sites by the cathode ray vectorcardiograph machine. This is owing in part to the relatively low film or paper speed of the electrocardiogram compared to the cathode ray trace of the vector loop, which is far more accurate and detailed from instant to instant.

The basic tenet of vectorcardiography is that all the electrocardiographic leads recorded in man are derivatives of the spatial cardiac vector, i.e., projections of the vector on the individual leads.[110, 119, 120, 136] Furthermore, the potential differences recorded at any electrode site from moment to moment are determined by the summation of all the

electromotive forces generated by all parts of the heart from moment to moment, i.e., by the spatial vector, they are not essentially or chiefly reflections of local subjacent myocardial potentials (proximity potentials). On the other hand, according to the concept advanced particularly by Wilson,[147, 150] unipolar precordial leads are semidirect leads and are determined largely by local electromotive forces generated in the subjacent region of the myocardium.[16] Thus right precordial leads are considered to be determined to an important degree by the underlying right ventricle. The occurrence of localized changes in the precordial leads has been regarded as evidence supporting the Wilson concept of proximity potentials. However, corresponding mirror image electrocardiographic changes observed in electrocardiograms recorded from a distant and predictable site,[14] cast doubt on the concept of a localized generation of the local precordial pattern and favor the concept that the changes represent the projection at the electrode site of the spatial cardiac vector.

The Spatial Cardiac Vector

Since the heart which generates the electromotive forces and the surrounding conducting tissues (volume conductor) is three dimensional, the vector representing these forces is oriented in three dimensional space, not in a single plane. In other words, the instantaneous vectors of cardiac electrical activity are spatial vectors and their ends may be represented by a loop which lies in three-dimensional space. We have no method of directly recording these actual instantaneous spatial vectors or the loop formed by these vectors, although devices are available for direct visualization of the three-dimensional relationships of the planar vectorcardiograms, or for direct stereoscopic recording of the vectorcardiogram.[105, 111] If our assumptions underlying vectorcardiography are correct, there is only a single actual spatial vectorcardiogram of a given heart at a given time, and the spatial vectorcardiogram determined from the vectorcardiograms in any two planes should have the identical magnitude, sense and direction regardless of electrode placement or other technicalities of the different methods of vectorcardiography.

By means of electrodes arbitrarily placed within the electrical field of the contracting heart, i.e., on the body surface and connected to appropriate recording galvanometers, we tap and record that component of the actual spatial vector which is directed toward the electrodes in question. The recorded component of the spatial vector is modified by the distance from the actual electromotive forces represented by the spatial vector and by the intervening conducting media, as well as by the instrumental devices for receiving and recording the electrical forces. For these reasons neither conventional electrocardiograms nor vectorcardiograms as now determined can be regarded as the true representation of the actual cardiac electrical forces, since these curves are dependent largely on the position of the receiving electrodes which only pick up a modified component of the actual instantaneous spatial vectors. Different systems of vectorcardiography represent different components of the true vector depending on their differences in electrode placement. Like many objects in space, the actual spatial vector may appear different when viewed from different directions; the actual spatial vector, if it could be determined, like the object viewed, should remain the same. Spatial vectorcardiography, as now practiced, refers to the representation of vector loops as projected onto multiple planes, usually the frontal, horizontal and sagittal. The spatial vector may be constructed from these planar vectors, but such constructions do not yield the true spatial vector, probably because some of the premises underlying the various techniques of vectorcardiography are more or less inaccurate (p. 44).

The symbol for spatial vector of the electrical forces of the heart is $s\hat{E}$, s for spatial, E for electrical forces, and the arrow head to denote a vector quantity. The spatial vector loop representing the ventricular electrical forces of depolarization is indicated by QRS $s\hat{E}$ loop, the spatial loop of repolarization by T $s\hat{E}$ loop, and the spatial loop of atrial depolarization by P$s\hat{E}$ loop.[illegible] The symbol s is omitted when referring to the planar vector loops, e.g., the horizontal plane QRS $\hat{E}$ loop.

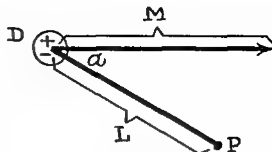
The Dipole Theory and Vectorcardiography

The electrophysiologic basis of the electrocardiogram described above (p. 18) applies equally to the vectorcardiogram with some change in terminology. A dipole has been defined as a pair of electrical charges of equal strength and opposite polarity, a

finite distance apart When a dipole is placed in a conducting medium (volume conductor) it produces an electrical field in that conductor Vectorcardiography is based on the premise that the electrical behavior of the heart and its effect on the surrounding body tissues are analogous to those of a dipole in a volume conductor

For the purpose of calculating the electrical potential at any point in the electrical field produced by a dipole in a volume conductor, we define the vector of the dipole as a vector whose direction is indicated by an axis drawn through the poles from the negative to the positive and whose magnitude is equal to the product of one of the charges by the distance between the two charges (poles)[110] Then the electrical potential at any point P in the electrical field (relative to a distant point) (Fig 16) is computed as being proportional to the magnitude of the dipole vector (M) multiplied by the cosine of the angle formed by the dipole vector and a line drawn from the dipole to point P (angle alpha) and inversely proportional to the square of the distance of point P from the dipole (L) It is essential to stress that this computation may be applied only if the distance between the charges of the dipole is small relative to the distance of point P from the dipole If the line from the dipole to point P is a right angle the electrical potential is zero as the angle alpha diminishes from 90 to 0 or increases from 90 to 180 degrees the potential increases correspondingly but with different polarity

In the course of depolarization and repolarization of the innumerable cardiac fibers not one but multiple dipoles are formed[1,2] However if there are many dipoles in a volume conductor the individual dipole vectors may be added by the parallelogram law to give a single total dipole vector Then at any point P in the electrical field produced by such multiple dipoles, the electrical potential (relative to a distant point) may be computed from this total dipole vector in the same way as the potential was shown above to be computed from a single dipole vector In other words the electrical field produced by multiple dipoles within a volume conductor is the same as would be produced by a single dipole whose dipole vector is equal to the sum of the individual dipole vectors But such vectors can be added only when they define concentric dipoles i e, dipoles with the same



Potential at P = $\frac{M \cos alpha}{L^2}$

D = Dipole
P = Point in Volume Conductor
M = Magnitude of Dipole Vector
L = Distance point from Dipole
a = Angle formed by M and L

Fig 16 Electrical potential at point P in an electrical field produced by a dipole (D) in a volume conductor M = magnitude of dipole vector a = angle alpha L = distance of P from dipole Potential at P = $\frac{M \cos alpha}{L^2}$

center Also it must be stressed again that these computations apply only if the distance between the multiple dipoles is negligible compared to the distance from the dipoles to the point P in the volume conductor

Vectorcardiography assumes that the electrical field set up by the hypothesized numerous dipoles of cardiac electrical activity in the tissues surrounding the heart (volume conductor) is the same as that which would be produced by a single dipole whose vector is the sum of these individual dipole vectors Thus the dipole theory applied to vectorcardiography assumes that the potential differences at points where electrodes are placed on the body's surface, i e points in the electrical field, are produced by cardiac activity as if the heart were a single dipole, and that these electrode sites are sufficiently distant from the dipole relative to the distance between the charges of the dipole or relative to the distance between the innumerable dipoles of cardiac activity

The Mean Electrical Axis and Angle of Deviation

It has been mentioned that the numerous electromotive forces generated by cardiac activity in various parts of the heart from moment to moment possess magnitude and direction and may be represented as vectors The resultant of these electromotive forces at

any instant may likewise be represented as a vector and is termed *the instantaneous electrical axis of the heart* The instantaneous axis of greatest magnitude is the major instantaneous axis of the heart The *mean electrical axis* is the representation of the mean magnitude and the average direction of the varied electromotive forces developed throughout depolarization and repolarization [8] Thus the mean electrical axis is determined by the duration as well as the amplitude of the electromotive forces The mean electrical axis of the QRS complex is the average of the instantaneous electrical axes of the QRS, the mean electrical axis of the T wave may be similarly considered The mean electrical axis of the heart is a vector in three-dimensional space (spatial vector s$\hat{E}$) but conventionally we have been concerned with the electrical axis as projected onto the frontal plane The major instantaneous electrical axis or the mean electrical axis projected onto the frontal plane may be calculated from the limb leads with the aid of the Einthoven triangle, the vector representation of the axis determined in this manner from the limb leads is termed the *manifest vector* and the voltage of this vector is termed the *manifest potential* [111] The angle (termed alpha) made by this manifest vector in the frontal plane with a horizontal line is called the *angle of deviation* of the electrical axis Einthoven thought that determination of the electrical axis would aid in distinguishing electrocardiographic abnormalities due to changes in cardiac position from those due to intrinsic myocardial disease but it has proved to be chiefly of theoretical value rather than of help in practical diagnosis

Determination of Electrical Axis

Determination of the mean electrical axis of the heart is often approximated by determination of the manifest *maximum instantaneous vector* from the limb leads by means of the Einthoven triangle the triaxial reference system or some other set of coordinates (Fig 17)

1 **Einthoven's Triangle** A circle is circumscribed about the Einthoven equilateral triangle, whose *apices represent the right and* left arms and left leg and whose sides denote the three limb leads The circumference is marked off in degrees with 0° at the three o'clock point and ±180° at the nine o'clock point of a transverse diameter and minus 90° at the upper and plus 90° at the lower end of the vertical diameter The center of the triangle (and circle) is the origin of the line vector representing the maximum instantaneous (or the mean) electrical axis The angle alpha made by the electrical axis with the transverse diameter is the angle of deviation The axis is determined from any two leads but it is best to use those with the most distinct R and S waves Ideally the leads should be taken simultaneously but conventional electrocardiographic leads may be used for rough approximations

The algebraic sums of the maximal amplitudes of R_1 and S_1 in millimeters is plotted on lead I (Fig 18) positive values being marked off from the midpoint of the line toward the 0° end (left arm) and negative values toward the 180° end (right arm) Similarly the algebraic sum of R_3 and S_3 (or R_3 Q_3 and S_3) in millimeters is plotted on the line representing lead III positive values going below and negative values above the center of the line

From these plotted points on any two lead lines perpendiculars are erected on the lead lines and extended until they meet A line drawn from the center of the triangle to this point of intersection is the vector of the maximal instantaneous electrical axis If this line vector is extended to the circumference the axis deviation from the horizontal may be read off the circumference in degrees Similarly the maximal instantaneous axis and angle of deviation of the T wave may be determined

The *mean electrical axis* of the QRS may similarly be determined, but the area of the QRS in any two leads is used instead of the peak amplitude The area of the QRS is measured in microvolt seconds each square of the electrocardiograph paper representing 0 04 microvolt second or 1 unit These areas (divided by time) denote the mean electromotive force of depolarization in those leads Similarly the areas of the T wave in any two leads may be plotted on two sides of the Einthoven triangle and the mean electrical axis of the T wave determined

The normal mean electrical axis lies between *0° and plus 90° Left deviation of the* electrical axis is indicated when angle alpha is between 0° and minus 60° or more while right deviation of the electrical axis is indicated when the angle of deviation is between 90° and 150°

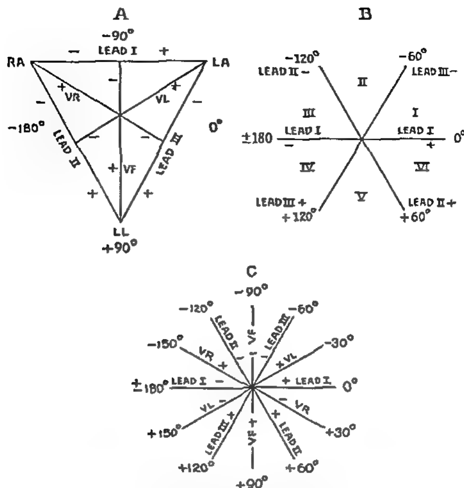


Fig 17 Coordinates to determine electrical axis of heart *A* Einthoven triangle *B* Triaxial reference system *C* Hexaxial reference system to include unipolar limb leads

2 The Triaxial Reference System[93] A circle is drawn with a horizontal diameter and two oblique diameters passing through the center at 60° angles to each other (Fig 19) The three o'clock end of the horizontal line which represents lead I is labeled 0 the nine o'clock end ±180, the oblique diameter running from above downward toward the 0 side represents lead II and is labeled −120 above and 60 below the oblique diameter running from above downward and toward the 180 side represents lead III and is labeled −60° above and 120 below

As directed above in the use of the Einthoven triangle the amplitudes of R_1 and S_1 and of R_3 and S_3 in millimeters are plotted on two of the lead lines beginning at the center of the system and going toward the 0 point or downward for positive values or toward the 180 point or upward for negative values For the mean electrical axis the *areas* of QRS in leads I and III (or leads I and II etc) are similarly plotted Perpendiculars to the lead lines are erected at the plotted points and extended until the perpendiculars intersect The maximal instantaneous axis or the mean electrical axis is represented by the line drawn from the center to this point of intersection Extension of this line to the circumference of a circumscribed circle marked off in degrees will disclose the angle of deviation of the electrical axis

The chart of Dieuaide[107] is also used to determine the mean electrical axis based on the same principles

Derivation of the Vectorcardiogram from the Electrocardiogram

If instead of a single instantaneous axis a series of such axes or vectors were inscribed as above e g every 0 01 second of the de-

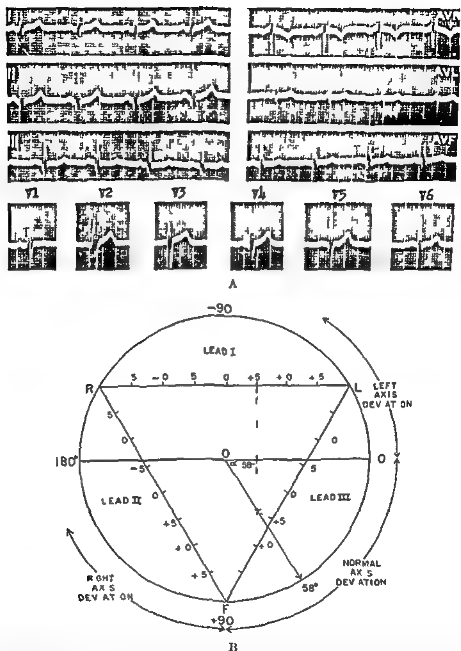


Fig 18 *A* Normal electrocardiogram Standard leads on left Augmented unipolar limb leads on right Unipolar precordial leads below R taller than S in V_1 R increases to V_4 and then diminishes Transition point between V_3 and V_4 Q absent in V_1 diminutive in V_5 and V_6

B Einthoven s triangle with representation of normal electrical axis of QRS in electrocardiogram in Fig 18*A* Angle of deviation 58 R_1 (6) $-$ S (1 0) = 5 R_2 (12) $-$ Q_2 (2) = 10 R_3 (7) $-$ Q_3 (2) = 5 It is assumed the leads were taken simultaneously

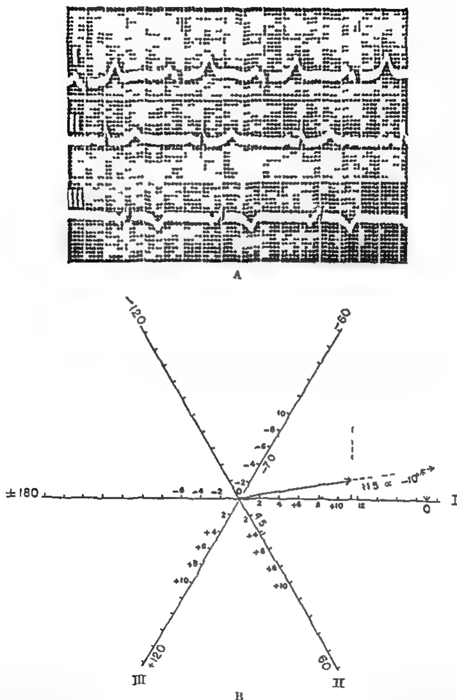


Fig 19 4 Left axis deviation due to horizontal electrical position of the heart Tall R_1 small R_2 deep S_3 P_3 and T inverted

B Triaxial reference system with representation of electrical axis of QRS in Fig 19 4 R_1 (13) − Q_1 (1 5) = 11 5 R_2 = 4 5 R_3 (1 0) − S_3 (8) = −7 It is assumed that simultaneous leads were taken The angle of deviation from the horizontal (−10) denotes axis deviation to the left of normal

polarization process (QRS) and the ends of these line vectors were joined the vectorcardiogram loop projection on the frontal plane would be obtained Such a loop can be constructed with the aid of the Einthoven triangle the triaxial reference system or by employing rectangular coordinates[119] The latter may be used to construct the horizontal and sagittal plane as well as frontal plane projection of the spatial vector loop

A simple method of vectorcardiographic derivation from the electrocardiogram utilizes rectangular coordinates i e horizontal and vertical axes crossing each other at right angles The horizontal line is positive to the left of the zero (observer s right) and negative to the right of the zero The vertical line is positive below and negative above the zero

The *frontal plane projection* of the vectorcardiogram may be constructed from lead I (represented on the horizontal axis) and lead aVF (represented on the vertical axis)

The *horizontal plane projection* is constructed on the rectangular coordinates by representing lead I on the horizontal axis and V_1 *on the vertical axis*

The *sagittal plane projection* is constructed on the rectangular coordinates by representing lead V_1 *on the horizontal axis and* aVF on the vertical axis

The vertical lines on electrocardiographic paper mark off intervals of 0 04 second The voltage of the QRS is noted at each 0 01 second if possible or at least at each 0 02 second Thus the voltage at at least four and possibly eight points would be measured if the QRS measured 0 08 second The voltage at the identical moments in each pair of leads is measured and recorded The lead to be represented on the horizontal axis is measured along the left or right according to the polarity and from the point reached on the horizontal axis the voltage in the other lead is now measured up or down on the vertical axis Thus each set of voltages *at identical instants* in the two leads defines a point to the right or left of the vertical and above or below the *horizontal* axis The line drawn *from the zero* to this point represents an instantaneous vector When the several vectors have been constructed at successive moments the line joining their ends is the derived vector loop in the given plane

Various methods have been utilized to derive the vectorcardiogram from the electrocardiogram In general the frontal plane vectorcardiogram has been derived from and correlated with the standard leads or with the unipolar limb leads the horizontal plane vectorcardiogram with the unipolar precordial leads[99] and the sagittal plane vector cardiogram with the esophageal leads

Vectorcardiography by Cathode Ray Oscilloscope

The manual method of deriving the vector cardiogram first employed by Mann[114] (monocardiogram) and modified in various manners by Howard[1 5] Wil on and Johnston[115] Grant and Estes[119] and others is gradually being replaced by use of the cathode ray oscilloscope[119] as practical instruments are devised to obtain direct curves of the vector loops on film Following his early cathode ray oscilloscope to record such loops Mann[131] devised a galvanometer activated by three amplifiers each corresponding to the individual standard leads of the electrocardiogram which reflected a brilliant light spot which could be photographed and recorded as its course described a vector loop Since then progressively improved *cathode ray tubes amplifiers timing* devices and cameras have become available However their clinical usage except for research is still hampered by *their high cost* and insufficient evidence that they provide adequate practical advantages over the electrocardiogram to justify their additional expense and greater difficulty in handling

The cathode ray tube contains a filament which emits electrons and these are attracted to a positively charged grid with an aperture through which the electrons pass and impinge on a fluorescent screen within the cathode ray tube They thus produce a brilliant luminous spot which can be both visualized and photographed In traveling from the grid to the screen the electrons pass between a pair of vertical and a pair of horizontal plates within the tube The beam *of electrons and consequently the luminous* spot is deflected when there is a potential difference between either pair of plates When *the pair of vertical plates is activated by a* potential difference caused by the electromotive forces generated by cardiac contraction the spot is deflected in the horizontal direction (i e the X axis) and when the horizontal pair is activated, the spot is deflected in the vertical direction (Y axis) When both pairs of plates are simultaneously

activated the beam moves obliquely, its orientation to the horizontal (X axis) and vertical (Y axis) being determined by potential differences (voltage) and polarity The plates are so arranged that a positive potential difference produces a downward displacement on one axis or a leftward (or anterior) displacement on the other

The two cables of one of the two bipolar leads determining a plane are connected to an amplifier and thence to the two horizontal plates of the cathode ray oscilloscope Similarly the two cables from the poles of the other bipolar lead after amplification are attached to the two vertical plates of the oscilloscope During the course of cardiac contraction the luminous spot describes a progressive series of dashes which are located various distances above or below the horizontal and to the right or left of the vertical axis of the fluorescent screen of the oscilloscope The whole forms a succession of loops (P QRS and T) beginning and ending at the center as a rule First the P loop then the QRS and finally the T loop are inscribed The P loop formerly poorly inscribed is now being more clearly delineated by newer technical developments A loop is formed corresponding to atrial repolarization as well as one corresponding to atrial depolarization but the former is not satisfactorily recorded at the present time It is apparent that the cathode ray oscilloscope merely adds vectorally the electromotive forces of the two leads and the resulting vector loop derives its properties entirely from those two leads[106] However the technique of vector recording with the oscilloscope provides much more detail from instant to instant than does the conventional form of scalar recording with the electrocardiograph Phase relationship is maintained because the two polar leads are recorded absolutely simultaneously

The two lead connections attached to two pairs of plates result in projection of the cardiac vector in one plane Each pair of leads determining a different plane can be connected successively to the same two pairs of plates the different plane projections being then recorded in succession as the connections to the plates are altered by means of a switch The various pairs of leads may be connected to three pairs of plates in three different cathode ray oscilloscopes to obtain the three plane projections of the vector cardiogram separately There is also available a vectorcardiograph with three amplifiers which feed a triple cathode ray oscilloscopic arrangement, permitting the three plane projections of the cardiac vector to be observed or recorded simultaneously

Because of the relatively small potential differences induced by the heart's electromotive forces amplifiers to increase these voltages 50 000 to 250 000 times are employed with each set of plates in order that the electron beam between the plates should be deflected sufficiently—about ▮ to 4 inches on each axis of the screen For standardization a voltage of one millivolt is introduced into the input circuit of each amplifier and the sensitivity controls so regulated that the desired deflection is obtained A three-step amplification selector permits the choice of optimal amplitude for recording and different amplitudes may be used to delineate the P QRS and T loops Similarly, there are controls to regulate the focusing and intensity of the luminous spot the latter depending on the intensity of the current of electrons forming the beam, which can also be controlled

An electric tuning fork or oscillator circuit provides time-marking by interrupting the vector loop tracing and transforming it into a discontinuous series of dashes Ordinarily there are 300–600 cycles per second for the QRS loop, or more for special study 200 for the T loop and 100 per second for the P loop Interruption at the rate of 500 cycles per second denotes that each dash represents 0 002 second The interrupted segments of the loop are very close together when there is a gradual change in direction and magnitude of the instantaneous vectors and widely spaced when the changes are abrupt Since it is important to know the direction in which the vector loop is being inscribed, the interrupted dashes may be modified to a tear drop or comet shaped pattern with the tail end in the direction of rotation by combining the electrical tuning fork with a relaxation oscillator[146] (an imperfect square wave oscillator)

The permanent recording of the vector projections may be made simultaneously with a 4 by 5 inch cut film camera, with a shutter speed adjusted to 0 5 or 1 second, depending on the cardiac rate The use of 35 mm camera and film is more economical Usually the plane projection vectorcardiogram of a

single cycle is photographed. It is possible to use cameras which *automatically record the* vectorcardiogram as the loops are inscribed. Several still pictures may be recorded per second by means of a cam deflected mirror which follows a continuously moving film and snaps back to its original position through spring action. By disengaging the cam, records can be made on continuously moving film and the temporal relations of successive cardiac phenomena can be recorded. This can be utilized for records of arrhythmias, for distinct separation of the P, QRS and T loops and possibly for clearer delineation of the S-T vectors. Fluorographic emulsions or lino graph paper is suitable for recording. A number of photographic methods have been reported which use special electrical circuits to obtain stereoscopic records directly from cathode ray tubes for better study of spatial vectorcardiograms.

Reference Systems and Electrode Placement

The placement of electrodes is based on the idealized concept that the heart is a point source of electrical potential, that this is at the center of a homogeneous spherical volume conductor composed of the trunk of the body, and that the electrode sites on the surface of the sphere are equidistant from each other and equidistant and electrically remote from the electrical center, i.e., the combined cardiac dipole. Various methods have been described to obtain true orthogonal components of the heart vector, including a mathematical solution for two-dimensional and three-dimensional central terminals[1 5] based on the general theory of heart vector projection.[114] Various spatial geometric reference frames have been visualized, with the electrodes placed on the surface of this sphere in such a manner as to define an equilateral tetrahedron,[151] a cube[1 0] or a rectangle (double cube or rectangular parallelopiped).[110]

The equilateral tetrahedron reference frame has the advantage of employing the same electrode placement electric sites as the standard limb leads to define the frontal plane projection and thus of utilizing the information obtained from the equilateral triangle of Einthoven which is formed by these electrode sites.[90] In the tetrahedron reference frame the apices of the geometric figure are the shoulders and pubis (but the lead electrodes are placed on their extensions onto the right and left arms and left leg as in the standard leads) and the fourth apex (electrode site) is the so-called point of Arrighi, 2 to 3 cm. to the left of the seventh thoracic spine. This position is labeled V_B. The use of the limbs for three of the four electrode sites also provides the advantage of convenience of placement and easy reproducibility of electrode placement. The polarity of this system is so arranged that the positive terminus of the instantaneous vector is registered, i.e., the arrow on the vector points from the negative to the positive, which is from active toward resting cardiac muscle.

The other main reference systems are orthogonal, the component leads being parallel to the natural coordinate axes of the trunk and perpendicular to each other, i.e., the electrodes for the component leads are placed on the thoracic wall in a rectangular arrangement. The common form of orthogonal representation in this country is the cube. The cardiac electrical center in a spherical conductor is regarded as situated at the level of the fourth intercostal space and midway between the anterior and posterior margins of a sagittal plane passing through the body just to the left of the sternum. The cube is formed by eight points on the surface of the sphere (trunk). The electrodes of three bipolar leads are so placed on the thorax as to represent four of the vertices of the cube as equidistant from the electrical center as the anatomy of the body permits, and the connecting leads form three adjoining edges of such a cube.

In the cube reference frame used by Grishman[1 0] (Fig. 20), the *first electrode* with three cable connections is placed in the right posterior axillary line at the level of the second lumbar vertebra (Z^+, X^-, Y^-). This electrode represents one pole of each of the three bipolar leads used to obtain the horizontal, sagittal and frontal plane projections of the cardiac vector. It is not only the positive pole of the vertical (superior-inferior) lead (Z^+–Z^-), but also the negative pole of the sagittal (posteroanterior) lead (Y^+–Y^-) and the negative pole of the horizontal (right to left) lead (X^+–X^-).

The *second electrode* (Z^-) is also placed in the right posterior axillary line, but at a higher level, namely at the level of the right scapular spine, and represents the negative pole of the vertical (superior-inferior) lead.

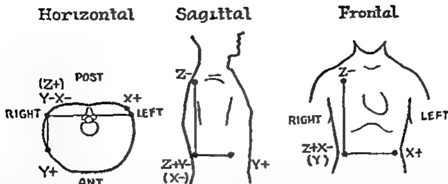


Fig 20 Cube Reference Frame Component bipolar leads of each vectorcardiographic projection showing sites and polarity of electrodes The electrode (X^- Y^- Z^+) is in the posterior axillary line at the level of L [illegible] vertebra and serves for each of the three bipolar leads The electrode X^+ is in the left posterior axillary line at the level L 2 The electrode Y^+ is in the right anterior axillary line at the level L 2 The electrode Z^- is in the right posterior axillary line at the level of the scapular spine Bipolar leads X^+–X^- and Y^+–Y^- determine the horizontal plane projection Y^+–Y^- and Z^+–Z^- the sagittal X^+–X^- and Z^+–Z^- the frontal plane

The *third electrode* (Y^+) is placed in the right anterior axillary line at the same level (L 2) as the first electrode It represents the positive pole of the sagittal (posteroanterior) lead (Y^+–Y^-)

The *fourth electrode* (X^+) is placed in the left posterior axillary line at the level of the second lumbar vertebra It represents the positive pole of the horizontal (right to left) lead (X^+–X^-)

Since in general the normal cardiac vector from negative to positive polarity is directed from right to left from above downward and from behind anteriorly, the electrode which is anterior to to the left of, or inferior to its mate in any bipolar lead is the positive electrode in that pair by arbitrary arrangement Each pair of electrodes determining a bipolar lead is connected with a pair of oscilloscopic plates of corresponding polarity, two bipolar leads (and correspondingly two pairs of plates) determine a given plane

The *frontal plane* of projection of the cardiac vector is determined by the horizontal (right to left) and the vertical (superior inferior) leads the *horizontal plane* by the horizontal (right to left) and sagittal (posterior anterior) leads and the *sagittal plane* by the sagittal (posteroanterior) and vertical (superior inferior) leads The body is viewed from the front for the frontal plane from above for the horizontal plane and from the right side for the sagittal plane projection of the cardiac vector Right left anterior and posterior refer to the body and not to the viewer Similarly in representations of the cardiac vector projections on paper or film, the left side of the body is on the right side of the paper in frontal and horizontal plane projections The lower side of the representation of the horizontal plane projection denotes the anterior aspect of the body, while in sagittal plane projections the right side of the paper denotes the anterior aspect of the body

One of the advantages claimed for the cube and other orthogonal systems of electrode placement is that the horizontal plane projection of the spatial vectorcardiogram conforms fairly closely with that predicted from the precordial lead electrocardiogram and vice versa while the frontal plane projection conforms with the standard lead and the sagittal plane projection with esophageal lead electrocardiograms On the other hand the need to place all the electrodes on the trunk renders this system somewhat less convenient and the site of placement less reproducible than in the tetrahedron system in which three of the leads are in the standard positions on the extremities

For other reference systems and methods of electrode placement the reader is referred to Duchosal and Sulzer[110], Schellong[140] Burger and van Milaan[10], Donzelot et al [105] The last named obtained vectorcardiograms by using the unipolar lead V_6 as the horizontal lead V_F as the vertical lead and V as the sagittal (posteroanterior) lead V_6 and V_F determined the frontal plane projection V_6 and V_2 the horizontal plane and V_F and V_2 the sagittal plane projection Lamb and Dimond[12] advocated a reference system combining some elements of the tetrahedron and of the orthogonal systems Other devices and

methods of electrode placement have been utilized in an effort to correct or reduce the errors inherent in systems now being used.[90a, 115]

If the different systems are all valid, the spatial vectorcardiogram of any individual at a given time should be invariant regardless of the system used. Nevertheless, considerable differences are found in the form and principal axis of the vector loops, in their spatial orientation, in the quadrants they occupy or in their sense of rotation.[103, 127, 115] As a rule, the differences with the various methods of electrode placement are greater in the horizontal and sagittal plane projections than in the frontal, and more marked in abnormal than in normal hearts.[103, 127]

The variations in vectorcardiograms observed with the different reference systems are due to various degrees of inaccuracy in the assumptions underlying vectorcardiography.[114] The heart is not a point source of electrical potential.[114, 14] The electromotive forces are dispersed in the cardiac generator and it is uncertain whether addition vectorially of the multiple electromotive forces permits the establishment of a unitary resultant or vector.[131, 111] If there is a single instantaneous vector, it is uncertain whether its origin is constant or whether it alters its position during the cardiac cycle.[109] Neither the human body nor its trunk is a tetrahedron, cube or parallelopiped, and the electrical position of the heart is eccentric, not in the center of the volume conductor.[139, 113, 117, 136] The conducting tissues (volume conductor) do not form a sphere or other symmetrical geometric figure nor are they homogeneous.[118] Other reasons for differences in the vectorcardiograms depicted by the various systems of electrode placement are: the electrodes are not equidistant from each other, nor are they placed at equal distances from the heart as the methods assume; the dimensions of the heart are not inappreciable relative to the dimensions of the volume conductor, and consequently the electrodes may be insufficiently remote electrically from the heart and may be affected significantly by adjacent local cardiac electromotive forces. These imperfections affect one system of electrode placement more than another or in one respect more than another. These deficiencies should be regarded as imperfections, for the most part quantitative imperfections, but they do not invalidate the entire study of vectorcardiography or any of the major systems of reference, since vectorcardiography is providing a useful body of theoretical and practical information regarding cardiac activity and cardiac disease.[1, 8] The need for universal agreement on a standardized method of electrode placement is apparent, but until the most accurate leads are determined, such standardization may be premature.[illegible]

THE NORMAL VECTORCARDIOGRAM

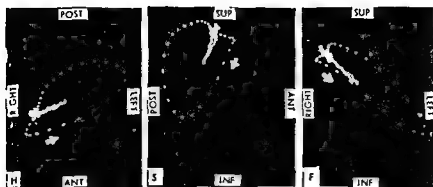
It is impractical at the present time to set down in detail the appearance or appearances of the normal vectorcardiogram in all the usual plane projections because significant differences are observed with different reference frames and different sites of electrode placement employed in the various systems of vectorcardiography. For the purpose of orientation, however, a brief résumé follows of the usual normal configuration of the vectorcardiogram, based chiefly on the method with which I am most familiar, that utilizing the cube reference frame and electrode position placement of Grishman.[10]

The QRS sÊ Loop

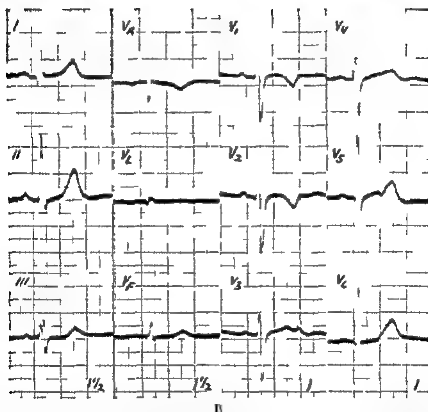
There are three recognizable vectorcardiograph loops, the P, QRS and T, of which the QRS loop is the largest. The QRS loop usually possesses a smooth, narrow, ellipsoid configuration, but is sometimes flattened or indented. It is usually three to four times as long as it is wide. The initial portion is inscribed slowly (markings somewhat closely spaced), the major portion of the loop more rapidly, and the terminal portion relatively slowly. The loop begins and ends at the same central zero point and is therefore closed. It is usually oriented to the left, inferiorly and slightly posteriorly, corresponding somewhat to the anatomic axis of the heart according to Duchosal and Sulzer.[110]

According to Burch et al.,[99, 89] who used the equilateral tetrahedron reference frame, there are two main QRS spatial loop patterns. Almost 90 per cent have a narrow elliptoid configuration with most of the area anterior to the isoelectric point, whereas somewhat more than 10 per cent have a second more complex configuration with length and width more nearly equal and the terminal portion of the loop located posterior to the isoelectric point. This division into two types of patterns is probably an artefact and due to proximity of the back electrode to the heart.[117, 90]

The normal vectorcardiogram with the



A



B

Fig 21 *A* Vectorcardiogram (VCG) of normal adult H horizontal projection S sagittal projection F frontal projection The vectorcardiogram is directed to the left inferiorly and somewhat posteriorly Counterclockwise inscription of QRS loop in horizontal plane (white arrow)
B Electrocardiogram (at 50 mm per second) of same subject

cube reference frame appears as follows[141-146] (Fig 21)

In the *horizontal plane* the loop is inscribed *counterclockwise* beginning with an initial deflection anteriorly and to the right and proceeding thereafter to the left and somewhat posteriorly The long axis in the adult is usually within the −30 to +30 degree segment and more often within the −10 to +10 segment

In the *sagittal plane* (viewing the right lateral aspect of the body) the QRS loop is inscribed *clockwise* and is characterized by a small initial deflection anteriorly and occasionally superiorly but the remainder is directed downward and somewhat posteriorly In the adult the QRS loop is usually oriented in the +90 to +120 degree segment but there is considerable variation and sometimes the QRS loop in this projection is

bizarre and a distinct long axis cannot be determined

In the *frontal plane* the QRS loop is usually inscribed in a clockwise direction when the loop lies within the +30 to +80 degree segment and counterclockwise when the loop lies within the +30 to 0 segment Most frequently the loop lies in the +15 to +70 segment The normal QRS loop in the frontal plane is inscribed to the left and downward but there may be an initial small deflection to the right and superiorly The QRS loop often appears very narrow in this plane and occasionally has a figure 8 configuration

Effect of Age and Respiration During the first week of life the QRS spatial loop is situated to the extreme right and somewhat posteriorly[133 138], in young children it assumes a more anterior orientation ultimately appearing as a vertical loop but extending more anteriorly and to the right than in adults In young children the initial portion may be large and may extend appreciably to the right[141] accounting for prominent R waves in right precordial leads As in adults the inscription of the QRS loop in children by the cube system is counterclockwise in the horizontal and clockwise in the sagittal and *frontal planes* *With advancing age the QRS* loop becomes progressively more horizontal and posteriorly located[1 0 ■]

With inspiration the QRS sÊ loop was reported to shift somewhat posteriorly and with expiration anteriorly[1 0] However Burch et al[101] noted that in pregnancy a deep inspiration caused the maximal vectors to become more anteriorly located The loop also tends to become more vertical with deep inspiration and more horizontal with deep expiration but little change occurs in the configuration of the loop There is evidence that the spatial position of the initial and terminal vectors of the QRS loop varies with the position and degree of rotation of the heart[154]

The T sÊ Loop

The spatial T loop, like that of the QRS, is ellipsoid but narrower and much smaller in size occasionally it is more circular[104 110 141] It is roughly parallel to and usually enclosed by the larger loop (Figs 21–22) The direction of inscription of the T loop is the same as that of the QRS in all three projections but it is inscribed more slowly especially the centrifugal (initial) limb[122]

In the adult the T loop in the cube *reference frame is usually located slightly an*terior to the right and inferior to the QRS loop from which it deviates usually by 10 to 30 degrees, but not more than 50 degrees[111] This constant positional relationship is important since wider divergence often denotes myocardial disease or other abnormality In children this spatial relationship between the T and QRS loops is much more variable than in adults, corresponding to the greater variability of the T wave in the electrocardiogram of children notably in precordial leads The T loop in children usually lies inferior and posterior to the QRS loop The backward direction of the T loop in infants and chil*dren corresponds to the inverted* T waves observed in leads V_1–V_4 In the first 24 hours of life the T vector is directed to the right or is vertical

The P sÊ Loop

Technical difficulties of recording this loop have led to neglect in studying it Conway et al[104] described the P wave as small and irregular or mitten shaped as being slowly inscribed and as occupying a position more or less parallel to the QRS More recently study of the P loop has been made feasible by means *of great amplification e g , at a sensitivity of* 30 to 45 cm /mv instead of the conventional sensitivity of 5 5 to 10 cm /mv Clear images of the P wave have been obtained with the aid of a rapid sequence automatic camera Hellerstein et al[123] have described a technique of selective (differential) vectorcardiography permitting systematic study (dissection) of the component P QRS and ST T loops of the cardiac cycle, which yields clear details of the P loop, as well as of the ST-T and initial and terminal parts of the QRS The vectorcardiograph (oscilloscope) beam is extinguished during all parts of the cardiac cycle except where the selective dissector apparatus unblanks the portion of the vectorcardiogram which is to be inscribed and studied

Studies with the cube reference frame reveal the P wave as a narrow elongated nearly vertical hairpin shaped loop directed downward, beginning and returning to the zero (isoelectric point) (Fig 22) Its direction is little if at all to the left or right of the vertical axis or anterior or posterior to the horizontal axis In the frontal plane the direction of inscription is usually counterclockwise, rarely linear or figure-of eight It is principally

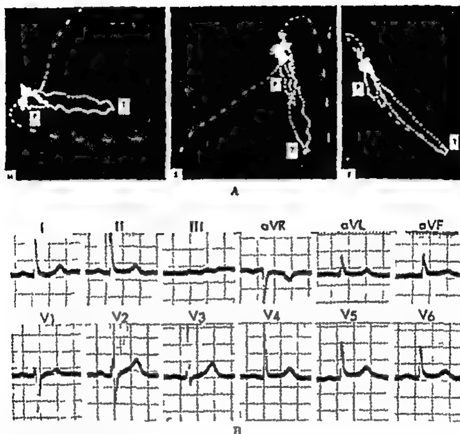


Fig. 27 *A* Vectorcardiogram showing normal P loop of 22 year old girl P loop is directed almost vertically downward and very slightly anteriorly and to the left
B Electrocardiogram in same case

counterclockwise in the horizontal plane In the sagittal plane the inscription is usually clockwise or figure-of-eight In the frontal plane the angle of deviation (alpha) of the major P vector ranged between 60 and 93 degrees with a mean of 78 8° in the series of Fowler and Dorney[112] in the sagittal plane from 70 degrees to 100 degrees with a mean of 84° Thus the inclination is almost straight downward with minimal deviation to the left and anteriorly These loops are altered in configuration in cases of mitral stenosis with left atrial enlargement and in cor pulmonale with right atrial enlargement[145] (p 122)

Derivation of Electrocardiographic Leads from the Vectorcardiogram

Theoretically it should be possible to derive the various leads of the electrocardiogram from the spatial vectorcardiogram or its plane projections Occasionally such derived electrocardiograms are essentially identical with those actually recorded by electrocardiography and they are termed concordant But often there are significant discrepancies and the derived and actual electrocardiograms are termed discordant These discrepancies are due to the imperfections in the vectorcardiographic method already enumerated notably the heterogeneity of the conducting medium particularly in relation to electrode placement, the inequality of distances between various electrode sites and the electrical center of the heart a possible continuous change in the electrical center the insufficient remoteness of some of the electrode positions and the eccentric position of the heart in the reference frame[11, 19, 109, 153, 17]

Discordance is particularly frequent in the precordial leads especially in extremely vertical or extremely horizontal hearts Milnor et al[126] emphasized their finding that conventional precordial leads do not usually lie in the same transverse plane as the nullpoint

(electrical zero) as an important factor in accounting for discrepancies between the precordial electrocardiogram and that derived from the horizontal plane vectorcardiogram The problem of adequate electrical remoteness of the electrode from the heart applies particularly to the precordial leads which are regarded by many as semidirect leads i e they are sufficiently close to the heart to be influenced predominantly by specific local areas in the cardiac electrical field which are in subjacent proximity to the electrode [150, 102] This belief is supported by the common clinical observation that the precordial leads may disclose more or less localized areas of anterior myocardial infarction not revealed by leads from more distant electrode sites (But see Duchosal et al [110, 109] and Milnor et al [136]) The theoretical basis of the vectorcardiogram and the claim that electrocardiographic leads may be accurately derived from the vectorcardiogram presuppose that the electrode sites including those for precordial leads are equally and adequately remote from the heart contentions which have not been conclusively demonstrated Nevertheless the discordance between actual and derived electrocardiographic leads may involve only quantitative discrepancies which often do not impair the practical value of the information obtained

The electrocardiogram may be derived from the vectorcardiogram by superimposing the various plane projections of the vectorcardiogram on an axial reference system representing the electrocardiographic leads or more directly by inspection The frontal plane vectorcardiogram is used to obtain the unipolar or standard limb leads the horizontal plane projection to obtain the unipolar precordial leads and if desired the sagittal plane projection to obtain esophageal or intracardiac leads [110, 141] Milnor and associates[136] described a panoramic vectorcardiograph' which not only permits the observer to obtain any desired view of the spatial vectorcardiogram on a cathode ray oscilloscope by adjusting two controls but which also derives and presents scalar electrocardiograms representing projections of the vectorcardiogram on any single lead axis

The frontal plane vectorcardiogram may be superimposed on the triaxial reference system of Bayley in such a manner that the point of intersection of the lead axes coincides with the origin or zero point of the vector loop (Fig 23) The horizontal axis denoting −180° on the right (observer s left) of the zero point and 0° on the left of the zero point represents the bipolar lead I the oblique axis running from +60° below to −120° above represents the bipolar lead II and the oblique axis from +120° below to −60° above represents bipolar lead III Midway between each pair of these three axes are drawn three other axes that from −150° above to +30° below, representing the aVR axis from −30° above to +150° below the aVL axis and from −90° above to +90 below the aVF axis A series of successive points are noted on the QRS loop in the order of inscription starting from and ending on the zero point The projection (perpendicular) of each of these points onto each lead axis discloses the polarity and magnitude of the electrocardiogram at corresponding moments in the cardiac cycle The *lead I axis is positive to the left (observer s right) of the vertical axis* leads II and III are positive below and negative above the horizontal axis leads aVR and aVL are positive above while aVF is positive below the horizontal axis The electrocardiogram at successive points (instants) of the vector loop is upright in any given lead if its projection falls on the positive and downward if its projection falls on the negative side of the lead axis The voltage at that point (instant) is indicated by the magnitude of the lead axis where the projection falls The same method may be used to outline the T and P as well as the QRS waves from their corresponding vector loops

In the normal frontal plane vectorcardiogram (Fig 21) the initial inscription often proceeds slightly to the right and its projection is on the right or negative portion of the lead I axis therefore a downward or Q wave is inscribed in lead I of the electrocardiogram Its magnitude is small because the distance from zero to the intersection of the axes is small Later the vectors of the loop are perpendicular to the lead I axis and there is neither a positive nor a negative deflection, in other words there is an isoelectric interval As the major portion of the loop then proceeds to the left, its successive points are projected onto the positive portion of the lead I axis and an upright or R wave is inscribed If the loop near its terminus again crosses the negative portion of the lead I axis a short distance from

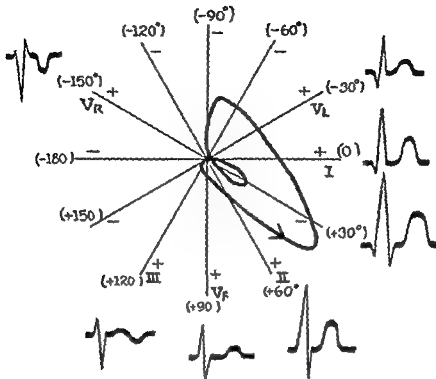


Fig 23 Standard bipolar and unipolar limb leads corresponding to and derived from frontal plane vector cardiogram superimposed on Bayley's triaxial reference system

zero a small S wave follows the R Since usually only a small initial portion of the loop is above the horizontal there is only a small Q wave in leads II III or aVF The major portion of the QRS loop being below the horizontal, it is projected onto the positive portion of leads II III and aVF, therefore the major deflection is upright in these leads i e an R wave follows the Q and is of greater magnitude If the terminal portion of the QRS loop is above the horizontal an S wave may also be inscribed in these leads If the vector at any point of the loop is perpendicular to a given lead axis its projection on the given axis at that instant is at the zero point and there is no electrocardiographic deflection i e it is isoelectric

The precordial leads may be similarly derived by superimposing the horizontal plane projection of the vectorcardiogram on an axial reference system representing the cross section of the thorax The origin of the loop coincides with the intersection of the axes and is placed either in the center or slightly to the left of center of the cross section The axes of the various precordial leads are then drawn from the center to the circumference corresponding to the site of placement of the precordial leads on the chest wall The projection of successive points of the loops on the various precordial leads is then determined (Fig 24)

The S T Vector and Segment

When the QRS loop is closed as it is normally the S T segment is isoelectric Just prior to ventricular depolarization the muscle surface is entirely positively charged and there is no potential difference Therefore the vectorcardiographic beam is at zero at the onset of the QRS loop and the electrocardiogram is at the isoelectric line Similarly, when there is complete depolarization the entire ventricular surface is negatively charged and there are no potential differences At this moment the QRS vector loop has reached its termination which is at the same zero point as the origin and the loop is closed Correspondingly the S T segment during complete depolarization represents no potential difference and is on the isoelectric line

When the QRS vector loop is open the S-T segment is above the isoelectric line in a given electrocardiographic lead when the open end of the loop is on the positive side of that lead axis the S T segment is depressed below the

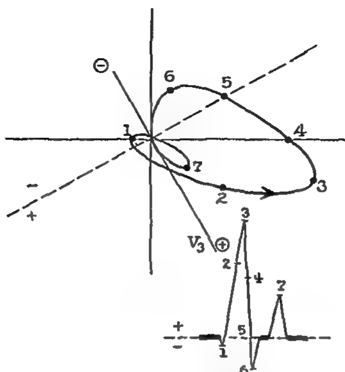


Fig 24 Derivation of a precordial unipolar lead V_3 from horizontal plane projection of vector loops QRS and T loops superimposed on rectangular coordinates with center (origin) of loop on zero point of coordinates Axis of derivation of V_3 drawn through origin of QRS loop Another line is drawn through origin perpendicular to this axis of V_3 Numbers indicate corresponding points on electrocardiogram and vectorcardiogram Amplitude of electrocardiogram deflections determined by size of projection onto V_3 axis Polarity determined by position below or above (left or right) interrupted line

isoelectric line when the open end of the loop is on the negative side of the given lead axis The distance between the point of origin and point of termination of the *open* QRS loop indicates the magnitude of the S T vector and the direction toward the terminus indicates the direction of the vector The S T segment is elevated if the vector is directed toward and it is depressed if the vector is directed away from the recording (positive) electrode, i e, the positive end of the lead axis

CLINICAL APPLICATIONS OF VECTORCARDIOGRAPHY

The clinical usefulness of the oscilloscope vectorcardiograph is as yet hampered by its costliness its cumbersome size and the necessary skill required in its use Furthermore extensive studies are still needed to correlate pathologic with vectorcardiographic findings The spatial vectorcardiogram is said to possess the advantage of presenting a unitary concept of the electrical field around the heart and of disclosing in a single curve all the findings in any electrocardiographic lead from any point or points of the body's surface whereas information by conventional electrocardiography is limited by the number of leads employed and by the position of the electrodes On the other hand it has been claimed that localized changes in the myocardium may not significantly affect the vectorcardiogram yet may be clearly disclosed in one of the precordial unipolar leads, which is in sufficient proximity to be modified by the subjacent myocardial change

Certain specific advantages in clinical practice have also been claimed for the vectorcardiogram over the conventional electrocardiogram More distinctive patterns of left and right ventricular hypertrophy have been disclosed by the vectorcardiogram and their identification is possible even in the presence of left or right bundle branch block Right ventricular hypertrophy may be more readily distinguished from right bundle branch block Patterns of myocardial infarction may sometimes be more distinctive in the vectorcardiogram than in the electrocardiogram

The pattern of acute myocardial infarction which is often obscured by bundle branch block in the electrocardiogram presents a distinctive pattern in the vectorcardiogram despite concomitant bundle branch block. These claimed specific advantages require further substantiation. For the present, vectorcardiography must still be regarded as a research technique.

VENTRICULAR GRADIENT[18, 81, 9, 100]

If the ventricular myocardium were absolutely homogeneous with respect to its metabolic processes and the generation of electromotive forces and if in consequence there was a uniform course, speed and duration of depolarization and an identical course, speed and duration of repolarization, the T wave would have the same voltage and duration as the QRS complex but would be oppositely directed (negative) and the areas under the QRS complex and under the T wave would add to zero. If the above conditions obtained except that the process of repolarization required more time than that of depolarization, the T wave would be oppositely directed to the QRS, their areas would be equal but the voltage of the T wave would be lower and its width (duration) longer than that of the QRS. Actually repolarization is slower than depolarization in the human heart, and the T wave is lower and wider than the QRS. But in addition, there are differences in ventricular metabolic and electrical activity, in consequence of which there are differences in the duration of depolarization in various regions of the ventricles. Repolarization occurs in some (subepicardial) portions *of the ventricle, while in other (subendo-*cardial) areas depolarization is not yet complete. These net differences in ventricular electrical activity of varying duration are termed the "ventricular gradient." Ventricular gradient has also been defined as "differences in the time course of the process of depolarization and repolarization representing mean deviation in the uniformity of the process of depolarization and repolarization," and also as "mean difference in duration of the excited state and net electrical effect of the differences in time course of the processes of depolarization and repolarization."

Since the course of depolarization is from the endocardial to the epicardial surface and since the subendocardial region remains depolarized longer than the epicardial regions, the effect of the ventricular gradient on the conventional electrocardiogram is to add a positive potential difference to the T wave which would otherwise have been negative if the duration of depolarization had been uniform throughout the ventricular muscle. The ventricular gradient converts the expected negative T wave into a positive one in almost all leads of the conventional electrocardiogram, except in those taken from some sites overlying the right ventricle or posterior aspect of the base of the left ventricle.

Since, omitting the effect of the ventricular gradient, the area of the T wave is equal to the area of the QRS but of opposite sign, any increase in the positive area of the QRS (e.g., due to ventricular hypertrophy, premature beats or bundle branch block) results in an equal increase in the negative area of the T wave, i.e., in its depth, duration or both. If the increase in T negativity is great enough it may more than neutralize the normal positive gradient and result in a negative T wave. Such negative T waves which are secondary to changes in the height or duration of the QRS (which in turn are due to alterations in the course of depolarization) are termed *secondary T wave changes*. If, however, there are fundamental metabolic changes in the muscle as a result of changes in blood supply or other injuries, there are alterations in the differences of duration and intensity of depolarization and the course of repolarization, i.e., the ventricular gradient is altered. If this is less positive than the normal, the T wave may be low or negative. Such a *negative T wave due to altered course of repolari*zation and not to alteration in depolarization (QRS) is termed a primary T wave change. Determination of the ventricular gradient reveals whether T wave alterations in the electrocardiogram are primary (gradient abnormal) or secondary (gradient normal).

The ventricular gradient may be represented as a spatial vector $s\hat{G}$, while its projection on a frontal plane is often represented by the vector $\hat{G}$.[100] The direction of the vector is from the area in which the mean duration of the excited state is greatest to the area in which it is least. Normally this is from the subendocardial to the subepicardial region. Unlike the conventional vectorcardiogram the ventricular gradient stresses the factor of

time, i e, duration of electrical potential differences as well as their intensity The ventricular gradient can be determined from the areas of the QRS and T waves since the vector of the ventricular gradient is equal to the sum of the vectors representing the QRS and T wave areas This can be determined by the parallelogram law The areas of the QRS and T waves in leads I and III are measured in microvolt seconds each square of the electrocardiograph paper representing 0 04 microvolt second or 1 unit when the paper runs at its conventional speed of 25 mm per second These areas represent the mean electrical force of depolarization

The area QRS_2 = area QRS_1 + area QRS_3 in simultaneous curves just as by Einthoven's theory $R_2 = R_1 + R_3$ If the areas of QRS of any two leads are plotted as microvolt seconds on the sides of the Einthoven triangle or in the triaxial reference system a vector is obtained $\hat{A}_{QRS}$ which represents the mean electrical axis ' during the entire period of the QRS (See p 35) Similarly by plotting the areas of the T waves in two leads, a vector $\hat{A}_T$ is obtained for the mean electrical axis throughout the entire period of T The mean ventricular gradient $\hat{G}$ (frontal plane projection) is obtained on the same triaxial reference diagram as the resultant of $\hat{A}_{QRS}$ and $\hat{A}_T$ by the law of the parallelogram of vector forces The value of determining the frontal plane ventricular gradient has been questioned[144] To obtain the spatial ventricular gradient $s\hat{G}$, it would be necessary to determine similarly the gradient projection on at least two planes among the frontal horizontal and sagittal Ivancic and Mikulicic[126] have described a method for determining and calculating the spatial ventricular gradient with the aid of anteroposterior horizontal and vertical bipolar transthoracic leads

An integrating circuit for the measurement of the areas of the waves has been devised[127, 96] It is probable that the cathode ray oscilloscope will replace the cumbersome manual derivation of the gradient vector as it has replaced manual derivation of the vectorcardiogram Perhaps then it will be possible to determine whether the ventricular gradient has any significant clinical application Thus far studies have been made of the positional relationship of the ventricular gradient $\hat{G}$ (or $\hat{A}_{QRST}$) to the vector of the QRS, $\hat{A}_{QRS}$ and to the anatomic position of the heart, and to determine whether T wave changes are due to primary myocardial disease[143]

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Chapter 3

BALLISTOCARDIOGRAPHY, PHONOCARDIOGRAPHY, CARDIAC CATHETERIZATION AND OTHER GRAPHIC METHODS

BALLISTOCARDIOGRAPHY

Ballistocardiography is a technique of graphic representation of the movements of the body imparted by the ballistic forces (recoil and impact) associated with cardiac contraction and ejection of blood and with the deceleration of blood flow through the large blood vessels[4, 6, 24, 8, 27] These movements quantitatively very minute are translated by a pickup device into an electrical potential which is suitably amplified and recorded on a conventional electrocardiograph machine During the recording the body must be completely at rest and relaxed in order to minimize bodily movements due to any other cause i e muscular contraction The ballistocardiogram should be taken with the patient as close as possible to the basal state at least an hour after smoking and in the absence of the recent administration of such drugs as Benzedrine It is usually recorded during quiet respiration but should also be taken during deep inspiration with the mouth open during full expiration and after mild exercise If direct body ballistocardiographs are used the patient must lie on a non elastic surface free of vibrations with a wooden block or sandbag supporting the heel at the Achilles tendon and a pillow under his head[29, 4] Other methods have been devised to minimize distortions due to the platform or surface on which the patient lies (infra)

The ballistic force which imparts movement to the body is a spatial vector which varies in magnitude and in direction in space throughout the cardiac cycle[29] Most of the ballistocardiographic techniques have recorded those forces which are exerted in the longitudinal axis of the body i e in the headward or footward direction Thus they record the projection of the instantaneous spatial vector along the longitudinal axis of the body But ballistocardiograms may be obtained of bodily movements due to force acting in a lateral direction or in various spatial directions and the ballistic motion in three directions may be simultaneously recorded[19, 22, 24, 25, 31] Dock[16] employed a spring opposed platform (65 by 55 cm with free side-to-side motion, contained in a frame which moved freely from front to back The thorax of the prone or supine subject was positioned on the platform so that lateral and dorso-ventral ballistocardiograms were obtained from the thorax alone Head foot ballistocardiograms were simultaneously obtained by an electromagnetic shin pickup These three dimensional techniques may better disclose certain information regarding blood flow than the conventional longitudinal ballistocardiograms

BALLISTOCARDIOGRAPH MACHINES

Two types of ballistocardiographic apparatus are generally employed (1) the type in which the patient is on a moving table and (2) the direct body type in which the apparatus rests on the patient's body, usually on the shins

Most of the pioneer observations were made with the high frequency, undamped ballistocardiograph of Starr,[52] which consisted of a hard movable table top supported by short strips of flat steel spring The subject lies supine on the table, to which are transmitted the impacts and recoils arising from cardiac contraction and the flow of blood The natural frequency of this table was about [illegible] cycles per second, which not only damped or eliminated the low frequency waves generated in the heart and great vessels, but also caused

amplitude distortion with respect to frequency, phase displacement and differentiating effects.[33]

Nickerson and Curtis[36] introduced a critically damped, low frequency table with a natural frequency of about 1.5 cycles per second. This, too, tends to cause phase and duration distortion of the ballistocardiographic waves and amplitude distortion with respect to frequency. Consequently there is a reduction in amplitude and increase in duration of the ballistocardiographic waves. High frequency components are not registered. Respiratory waves which are of low frequency, are well transmitted by this table and recorded on the ballistocardiogram causing a wavy baseline which distorts the record. Consequently it is desirable to suspend respiration during registration of the ballistocardiogram. The important effects of expiration and inspiration on the ballistocardiogram cannot be studied with this table.

The apparatus of both the Starr and Nickerson types is cumbersome, costly, not portable and therefore not generally available. Ballistocardiography has become a practical clinical procedure only since the availability of a simple portable and inexpensive apparatus introduced by Dock and Taubman.[18] By their method or modifications thereof, the patient lies supine on a fixed table or floor and a crossbar is placed across the shins. The impacts and recoils imposed on the body by cardiac contraction and the expulsion and flow of blood in the large vessels are translated into movements of the bar and thence into electrical potential by means of a photoelectric cell or electromagnet. But body frequency and damping cause distortions in the ballistocardiogram, which should be borne in mind when it is applied to physiologic or clinical studies.[56]

The artefacts and distortions of the ballistocardiographic tracing introduced by oscillations created by the body and its contact with a table or platform, not related to cardiovascular dynamics, have recently been critically reviewed by Talbot and Harrison.[54] To minimize these distortions Von Wittern[61] used a light suspended platform (pendular bed) of very low natural frequency, Talbot et al.[53, 15] placed the subject on a very light table floating in a pool of mercury (aperiodic ballistocardiograph), and Tobin et al.[59] devised an electrical method of filtering out body resonance distortions. Rappaport[35a] employed a bed weighing only 4 lbs. and with a natural frequency of less than 0.3 oscillations per second in order to minimize restraint of free body movement and to eliminate extraneous distortions of the ballistocardiogram.

PICKUP DEVICES

A great variety of pickup devices may be employed to obtain ballistocardiograms. They record either (a) the distance of body displacement, or (b) its velocity or (c) its acceleration caused by cardiac ballistic forces.

Photoelectric Device

The photoelectric device records displacement due to body motion, the latter causing movements of the crossbar which modifies the amount of light falling on a photoelectric cell either by passing between the light source and cell or by affecting a hinge which regulates the light. The photoelectric cell device is connected to the right and left arm cable terminals of an electrocardiograph machine and the ballistocardiogram is recorded with the switch selector on stardard lead I. Because of wide respiratory undulations of the photoelectric ballistocardiogram, an electrical filter is incorporated in the apparatus to reduce these swings.

Electromagnetic Pickup Device

The electromagnetic pickup device consists of an Alnico magnet producing a magnetic field and a coil of wire within the magnetic field, so arranged that magnetic lines of force are cut by motion of either the wire coil or the magnet transmitted through contact with the crossbar on the shins of the subject. These changes in magnetic lines of force result in electrical energy of varying potential which is transmitted through the coil of wire, the ends of which are hooked up to the electrocardiograph machine as described above. The electrical current generated is proportional to the *velocity* with which magnetic lines of force are cut. Thus this device records velocity of body motion, not the degree of displacement. Actually the unmodified electromagnetic device is too sensitive, and results in artefacts caused by even the slightest body tremor. It tends to exaggerate the high frequency ballistocardiographic waves. Consequently, condensers of 20 to 50 microfarads are usually inserted across the wire coils,[17] which tend to eliminate these distortions, but the resulting curves are altered so as to resemble the dis

placement records obtained with the photo electric cell If only a 2 microfarad condenser is inserted most of the oscillations due to muscle tremor are eliminated with retention of the velocity type of curve

Accurate timing of the ballistocardiographic waves may be obtained with 2 channeled electrocardiographs by taking a simultaneous electrocardiogram, phonocardiogram or radial pulse tracing With single-channeled machines timing is accomplished by attaching the electrocardiograph in series with the limb electrodes [22, 1] The electrodes are applied as for an electrocardiogram The left leg lead is detached from the left leg electrode and connected with the left arm terminal of the ballistocardiograph The detached left leg electrode is now connected with the right arm terminal of the ballistocardiograph The tracing is then recorded on lead II or lead III whichever has the taller RS complex

With either the photoelectric or electromagnetic device, the electrocardiographic sensitivity is set to give 1 cm deflection per millivolt and the pickup device has a sensitivity which results in maximum ballistocardiographic deflections of 2 to 3 cm in the normal young adult For more exact quantitative standardization a known force is imposed on the body (e g by striking the shoulder with a pendulum transmitting a known force) and the resulting deflection on the record is measured [18, 40, 48]

Acceleration Ballistocardiogram

For most accurate quantitative analysis of the ballistocardiographic waves a pickup dependent on the acceleration of body motion rather than on displacement or velocity is required For it is acceleration not displacement or velocity which is a measure of the force of motion imparted by the recoil of the heart and the impacts of blood ejected from the heart along the vascular system Acceleration ballistocardiograms have been obtained by apparatuses which electronically differentiate the velocity ballistocardiogram obtained with the electromagnetic pickup and thereby convert it into an acceleration ballistocardiogram [46, 9]

Elliot and associates [9] have developed an ingenious device for obtaining a direct acceleration ballistocardiogram The pickup or accelerometer operates on electrokinetic principles whereby electrical changes occur at the surfaces of contact of a mercury sulfuric acid interface (the so-called U effect) The pickup element is actually a capillary tube with alternate layers of mercury and normal sulfuric acid At each end of the capillary tube is a mercury seal into which a copper or platinum electrode is inserted Upon motion of the element, changes in electrical voltage are induced by changes in the mercury acid interfaces which are proportional to the change in contour of the interfaces and these in turn are proportional to the acceleration of imparted motion This accelerometer is readily calibrated for quantitative study of the ballistocardiographic waves by use of a simple pendulum Once calibrated its response can be standardized by use of the 1 millivolt standardization of the recording electrocardiograph The apparatus is simple and portable and is applied to the shins as is the Dock electromagnetic device

THE NORMAL BALLISTOCARDIOGRAM [6, 17, 21, 43, 4, 12, 41, 48]

The normal ballistocardiogram (BCG) consists essentially of a series of consecutive waves, termed H, I, J K L M N O etc, forming a distinctive pattern (Fig 25) The upward waves H J L N represent headward impacts or recoils of the body whereas the downward waves I K M, O represent footward movements The waves H through K occurring during systole are the most prominent and important The waves L to O are diastolic in time and of much smaller amplitude Corresponding waves occur in the lateral and dorsoventral ballistocardiograms [16, 34]

Atrial Ballistocardiographic Complex

Preceding the H wave is a group of smaller waves associated with the ballistic effects of atrial systole namely D E F G also termed atrial h i j, k These are alternately headward and footward waves respectively the D or h wave being due to recoil from atrial systole and E or i due to impact of filling of the ventricle Since the D wave reaches its peak at about 0 10 second and the E wave at about 0 25 second after the onset of the P wave of the electrocardiogram and the F and G waves may last up to 0 40 to 0 50 second after the onset of P it is apparent that most of the D E F G complex overlaps the systolic complex of the ballistocardiogram which begins 0 16 to 0 28 second after the onset of P Therefore the atrial ballistocardiographic waves may significantly modify the

II and I waves, increasing or decreasing their amplitude

Ventricular Systolic Complex

H is a small upward wave beginning 0 04 to 0 08 second after the electrocardiographic Q wave and lasting 0 05 to 0 07 second It coincides with isometric contraction[29] and may be due to headward motion of the atrioventricular septum and of the blood in the atria as the atrioventricular valves are tensed and moved toward the atria It may be due in part also to superimposition of the atrial J wave (J') It is improbable that it is due to atrial contraction because the H wave often persists during atrial fibrillation [14] Increased prominence of the H wave may be observed with myocardial disease and heart failure and in cases of hypertension

The I is a deep downward wave and the J a prominent upward wave which occur together during ventricular ejection The I wave is produced by the footward recoil of the body to the early systolic ventricular ejection of blood into the aorta and pulmonary artery By correlation with the electrokymogram the I wave appears to coincide with the beginning of the rise of the aortic wave The J wave is usually the most prominent wave of the ballistocardiogram and is caused by the headward impact of blood at the arch of the aorta and bifurcation of the main pulmonary artery In abnormal cardiac states the I wave may not be evident or it may be decreased in amplitude Similarly the J wave may be diminished in amplitude, slurred and notched, and its peak may be delayed to 0 28 second or more beyond the onset of the QRS, whereas normally the peak of the J occurs 0 22 to 0 26 second after onset of the Q wave

The K wave directed footward the last deflection of the systolic complex, occurs just prior to the second heart sound and is attributed to deceleration of blood flow in the aorta The aortic after fling and the impact of the blood on the smaller arteries also contribute to this wave It extends downward to the level of or slightly below the depth of the I wave The K wave is best recorded by the electromagnetic ballistocardiograph and varies with the type of instrument used Since slowing of the blood flow in the descending aorta by the peripheral resistance is largely responsible for the K wave its amplitude is greater and its slope steeper when the peripheral resistance is increased as in essential hypertension or when there is arterial inelasticity, as in arteriosclerosis of the aorta associated with aging The K wave is also deepened by increased flow in the descending aorta when the cardiac output is augmented by digestion exercise or pregnancy and it is decreased with diminished cardiac output in shock When there is shortening or obstruction of the aorta the K wave is small or absent as in aortic thrombosis or in coarctation of the aorta [7, 37]

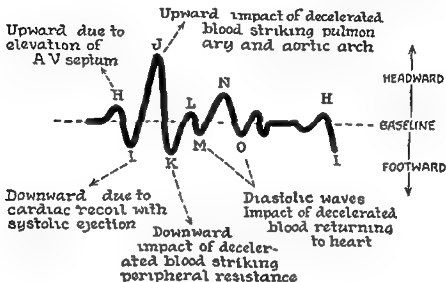


Fig 25 Diagram of ballistocardiographic waves and their origin

The I, M, N and other waves occur in diastole and are normally much less prominent than the systolic waves In three dimensional ballistocardiograms the waves following K are predominantly longitudinal suggesting that they are derived from forces directed along the aortic (longitudinal axis)[34] They may become quite prominent and even exceed the I and J waves in amplitude in conditions such as constrictive pericarditis heart failure or during the Valsalva experiment According to Tannenbaum et al[35] the L wave is part of the systolic complex since the nadir of the L wave corresponds to the dicrotic notch in the aortic and pulmonary artery electrokymograms The L wave is a headward deflection occurring during isometric relaxation of the ventricles and is presumed to be due to impact on the atrioventricular valves which are forced upward toward the atria

The M wave occurs during the early diastolic influx of blood into the ventricles and is a footward deflection due to the impact of blood impinging on the apex

The N wave is a headward deflection at the end of the early diastolic filling of the ventricles With arrest of the inflow as ventricular pressure rises there is a reflux toward the atrium and consequently the headward N wave

Effect of Respiration on the Ballistocardiogram

Marked variations in amplitude of the waves of the ballistocardiogram particularly of the I and J ejection waves occur during the phases of respiration[13] Normally the amplitude of the inspiratory I-J stroke was found to be less than twice that of the expiratory I J stroke in the electromagnetic ballistocardiogram[1] The waves increase in size with the onset of inspiration and diminish during expiration These phasic variations are more striking in older subjects than in young adults and also become exaggerated in the presence of cardiac disease The effect of respiration is attributed to its influence on the filling of the right ventricle and consequent right ventricular ejection

Thus the increase in amplitude of the I J waves during inspiration reflects essentially right ventricular activity Similarly during expiration reduction in amplitude of the I and J waves is related to a diminished contribution of the right ventricle to the ejection waves Therefore, abnormalities in left ventricular ejection may be observed best or only during expiration when the right ventricular component is minimized The Valsalva maneuver by interfering with venous return to the right ventricle and thereby diminishing its stroke output similarly magnifies the left ventricular component of the ballistocardiogram and its abnormalities of ejection as disclosed in the I and J waves The ballistocardiographic waves are diminished in amplitude during the Valsalva maneuver because of the reduction or loss of the right ventricular contribution

Studies of three-dimensional ballistocardiograms may alter or extend our concepts of the influence of respiration The *lateral* systolic IJ wave *increases* in size during expiration whereas the IJ decreases in amplitude with expiration in the *head foot* and *dorsoventral* ballistocardiograms[34] The increase in lateral IJ during expiration has been related to a rise in the diaphragm and apex of the heart with a change in the axis of left ventricular ejection

Effect of Exercise

Mild exercise increases the amplitude of the HIJK complexes in the normal subject without altering their configuration[33] But abnormalities do appear with increasing frequency after the fifth decade Exercise has been said to increase the incidence of ballistocardiographic abnormalities in patients with coronary artery disease or diminished cardiac reserve Occasionally abnormalities present in the basal ballistocardiogram may disappear immediately after exercise Tall L waves may be present briefly after strenuous exercise[17]

Effect of Aging

Progressive increase in age is associated with increasing frequency of abnormal ballistocardiograms in subjects who are presumed to be free of cardiovascular disease Beyond the age of 45 more than one third of apparently normal men and one fifth of apparently normal women have an abnormal ballistocardiogram beyond the age of 60 more than half of persons without apparent heart disease have abnormal ballistocardiograms[2] It is uncertain to what extent such abnormalities actually denote cardiovascular abnormalities which are not otherwise demonstrable

With increased age the I wave diminishes in height from about 5 mm at the age of 20 to 2 5 mm at the age of 60 while concomitantly

the J wave decreases in amplitude from about 8.5 to 5.5 mm. Consequently the ratio of the H and K waves to the I and J waves respectively is significantly increased.[50] Since many of the ballistocardiographic changes observed with aging are similar to those observed in cases of clinical coronary heart disease, it was suggested that the ballistocardiographic abnormalities associated with aging may actually be indicative of the increasing frequency of coronary atherosclerosis with age. On the other hand, studies with three-dimensional ballistocardiography have shown that with aging the lateral systolic IJ wave increases in amplitude while the head-foot IJ diminishes.[34] This is due to a more transverse axis of ejection because of the tortuosity and elongation of the aorta in older individuals.[18] Changes in the position of the heart and velocity of ejection may also be concerned with the large lateral IJ wave. Thus a diagnosis of an abnormal ballistocardiogram based only on a diminished head-foot IJ in older subjects is unjustified. An abnormal head-foot ballistocardiogram is more likely to denote cardiac disease in the younger adult than in the older subject.

Alterations in the ballistocardiogram have been described after smoking,[9, 25, 30] and digestion and in a variety of noncardiac conditions including obesity, orthopedic abnormalities, pulmonary disease, nervous states, parkinsonism, fever, hyperthyroidism, anemia and adrenal disease and as a result of technical factors.

THE ABNORMAL BALLISTOCARDIOGRAM

Abnormalities in the ballistocardiogram are characterized either by aberration in the appearance of the general pattern, by disturbance in the regularity of the sequence of normal waves, by changes in the absolute or relative size of the individual waves, or by several of these (Fig. 26). Changes involve essentially or exclusively (1) the systolic I-J-K complex in all beats or only during expiration, or (2) the H wave or the diastolic waves, or (3) there may be an exaggeration of the respiratory variation of the amplitude of the I-J deflections.

Classification of abnormal ballistocardiograms may be based on the criteria suggested by Brown and associates.[8]

Grade 1. Regularity and distinctiveness of pattern are preserved and inspiratory IJ

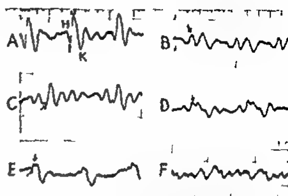


Fig. 26. Variations of abnormal patterns. *A*, Normal. *B*, Prominent H wave. *C*, Diminished I wave. *D*, Notched J wave. *E*, Small I wave and low notched J wave. *F*, Bizarre pattern. (Courtesy Dr. R. Taymor.)

amplitude is normal. The expiratory complexes vary, some showing diminished amplitude and loss of distinctiveness of the individual waves.

Grade 2. One half or more of the complexes are abnormal, chiefly during expiration, but the inspiratory complexes may also be diminished in amplitude. The J wave may be notched; I or K absent.

Grade 3. The amplitude is low in all complexes. Most of the complexes are abnormal both in expiration and inspiration with respect to regularity and definitive pattern but they are individually identifiable.

Grade 4. Totally abnormal complexes are present throughout. The complexes are all of low amplitude and unidentifiable. Grade 1 denotes minimal abnormality and may be due to extracardiac factors modifying the venous return or change in anatomic axis. The other grades indicate increasing degrees of abnormality.

Inspection of the ballistocardiographic record may disclose an exaggeration of the normal respiratory variations in amplitude of the I-J waves. A reduction of the expiratory amplitude to less than half of the inspiratory amplitude is abnormal and may be observed in older individuals and as a result of extracardiac factors, especially pulmonary emphysema or fibrosis. It is also observed in many patients with hypertension. When the majority of I-J deflections are thus abnormally small in expiration (Grade 2), and especially when these amplitude changes are associated with abnormal or bizarre patterns in expiration (Grade 3), the changes are prob-

ably associated with myocardial dysfunction But in older individuals whose ballistocardiograms are not bizarre in form, three-dimensional ballistocardiograms may show that the lateral IJ complexes are not small and do not decrease or even increase in expiration March[34] suggested that the tracing may be considered normal in the absence of bizarre complexes if the ratio

$$\frac{(IJ_{\text{Head foot}} + IJ_{\text{lateral}}) \text{ in expiration}}{(IJ_{\text{Head foot}} + IJ_{\text{lateral}}) \text{ in inspiration}} \times 100$$

is over 60

The amplitude of the systolic complex may be unusually high in patients with high cardiac output owing to such conditions as hyperthyroidism anemia and arteriovenous fistula even in the absence of cardiac disease The high amplitude persists in the high output heart failure associated with these diseases Low amplitude of the e waves may be observed in cases of severe myocardial disease shock myxedema adrenal and pituitary insufficiency but also in the absence of organic disease

Abnormalities of I J Complex (Fig 26 C F)

The I J complex especially the I may be decreased in amplitude absolutely and relative to the amplitude of the K wave The I wave may be slurred its peak blunted or notched, or it may be completely absent or obscured Similarly the J wave may be slurred or notched or its peak may be delayed Deep notching of the J wave may produce an M shaped pattern late in systole Notching of the J wave may be associated with a high take-off from the H wave I either being absent or appearing as a small notch These abnormalities may appear only and should therefore be sought in full expiration and the ballistocardiogram in expiration should be contrasted with that in deep inspiration

Abnormalities in the K Wave

Abnormality of the K wave may be characterized by increased depth and an early trough as in essential hypertension and aortic arteriosclerosis The deep K wave may then dominate the ballistocardiogram in contrast with the lesser amplitude of the I J waves

The K wave may be shallow or absent (cut off) in cases of coarctation of the aorta or aortic thrombosis with obstruction It is also decreased in shock The type of ballistocardiograph used must be considered in evaluating the amplitude of the K wave since the latter is deeper with the high frequency than the low frequency table, with direct body apparatus than with the table types and with the electromagnetic pickup than with the photoelectric

Abnormalities in the H Wave

The H wave may be greatly increased in height (Fig 26B), which may equal or exceed that of the J wave H and J waves of equal height separated by a notch, are common in coronary artery disease but occur also in cases of mitral stenosis hypertension heart failure and constrictive pericarditis Such complexes are described as fused H-J or 'M type' patterns They may become more evident or appear only during expiration

Duplication or splitting of the peak of the H wave may occur in cases of mitral stenosis with sinus rhythm or with atrial fibrillation Presumably rigidity of the mitral valve interferes during isometric contraction with the headward motion of the atrioventricular septum which is responsible for the H wave

Changes in the Diastolic Waves (L M N O)

Tall L waves are observed in a variety of diseases when these are complicated by heart failure They have also been noted in some cases of coronary disease of mitral stenosis, of myocarditis and after smoking

The L and M waves are often small and the headward N wave tall in cases of tight mitral stenosis, and in some cases of constrictive pericarditis[43] Tall N waves are often associated with L and M waves of high amplitude in cases of heart failure and protodiastolic gallop and in some cases of mitral insufficiency Deep O waves in the presence of tall L M and N waves may be observed with bradycardia in cases of high stroke output and atrial fibrillation and in aortic insufficiency

CLINICAL CORRELATIONS OF THE BALLISTOCARDIOGRAM

Although abnormal ballistocardiograms are found commonly in certain cardiovascular diseases, specific abnormal patterns cannot be attributed to localized anatomic lesions or specific etiologic diseases Abnormalities in the ballistocardiogram may denote abnormalities in systolic contraction and ejection of blood abnormalities in the propulsion of blood through the great vessels alterations in the position of the heart and axis of ejection of blood vascular changes resulting in abnormal response to the impact of blood masses, as well as abnormalities in transmission of these im

pacts and recoils through the body tissues and the ballistocardiographic apparatus. On the other hand, it must also be emphasized that the ballistocardiogram may be normal in patients with organic heart disease as in compensated rheumatic cardiovalvular disease after compensation has been restored to the failing heart, and occasionally in patients with angina pectoris or after acute myocardial infarction.[21]

Coronary Artery Disease, Angina Pectoris Myocardial Infarction[5, 11, 27, 3] **(Fig 27)**

Abnormal ballistocardiograms have been observed in over 90 per cent of patients with amplitude.[11] But even when the amplitude of the systolic waves is increased, normal wave pattern may not be restored. Although ballistocardiographic abnormalities are the rule in angina pectoris there is no characteristic pattern of angina pectoris or coronary artery disease, the changes observed do not differ significantly from those seen in patients with hypertension or various forms of myocardial disease.

Ballistocardiographic abnormalities are observed much more frequently than electrocardiographic changes in cases of angina pectoris without a history of myocardial infarction.

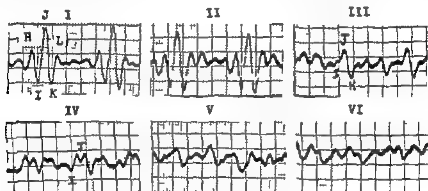


Fig 27 Ballistocardiograms in coronary heart disease
I Normal ballistocardiogram (BCG) in normal 41 year old white male
II Normal BCG in 64 year old man with history of acute myocardial infarction four years previously. Electrocardiogram shows evidence of old anterior wall infarction
III 69 year old man. Multiple acute myocardial infarctions. BCG shows very low amplitude of I wave
IV 69 year old man. Angina pectoris. Abnormal electrocardiogram. BCG shows low I wave and notching of J wave
V 67 year old man. Coronary heart disease. Blood pressure 190/100. BCG shows low I wave and poor definition of remaining waves
VI 50 year old male. Acute myocardial infarction one year previously. BCG shows bizarre pattern

angina pectoris at rest or following exercise. The abnormalities include increased respiratory variation in the I J deflections, low amplitude, notching or fusing of the H I-J complex or completely bizarre systolic complexes. The diastolic complexes show little or no change in the absence of heart failure. Abnormalities in angina pectoris may be present only in expiration or only after exercise or may be increased by these factors. Abnormal ballistocardiograms after smoking occur with much greater frequency in patients with coronary artery disease than in normal subjects.[11, 45, 30] Following the administration of nitroglycerin to patients with angina pectoris whose ballistocardiograms have been abnormal the low amplitude of H I J is increased, notched J waves may disappear, the I J stroke is lengthened, and L waves are reduced in amp-

farction. That these ballistocardiographic changes are significant appears to be suggested by follow up studies which disclose a surprisingly high incidence of subsequent coronary heart disease and mortality rate in subjects with abnormal ballistocardiograms who are otherwise apparently normal.[47, 10]

In cases of *myocardial infarction* the ballistocardiogram may be normal immediately after the acute attack or may show Grade 3 or 4 abnormality, including low amplitude of systolic waves, notching of J and fusion of H J. Very small or absent I waves, and small I with delayed J K segment, have been noted frequently. Even in those patients with normal tracings in the early period abnormalities almost always appear by the third to fifth week. Following the patient's recovery from acute myocardial infarction, his ballistocardio-

gram may revert to normal or show only Grade 1 changes or Grade 3 or 4 changes may persist[32] There is some evidence that the incidence of another myocardial infarction in a year or two or of sudden death is much higher in patients with asymptomatic healed myocardial infarction who ballistocardiograms show Grade 3 or Grade 4 changes than in those who ballistocardiograms are relatively normal[33] Thus abnormal ballistocardiograms in patients with coronary artery disease are regarded as being of value not only in suggesting or confirming the diagnosis of latent or clinical coronary artery disease but especially in prognosis[33, 50] But since hypertension which is frequently associated with an abnormal ballistocardiogram often accompanies coronary artery disease, an abnormal ballistocardiogram may have no diagnostic significance with respect to coronary artery disease in the presence of hypertension Similarly the ballistocardiogram may have little or no diagnostic value in coronary artery disease after the age of 45 because of the frequency of abnormal tracings after that age in apparently normal persons

Hypertension

The ballistocardiogram is normal in most cases of mild hypertension and in most hypertensive patients below the age of 25 When the tracing is abnormal it most often discloses an increased respiratory variation in the I J amplitude Brown's Grade 1 abnormality[33] Such abnormalities are usual in advanced or prolonged hypertension The K waves are usually deep in uncomplicated hypertension except when the hypertension is due to coarctation of the aorta The deep K waves are often associated with shortening of the I J stroke or absence of the I wave Sometimes the abnormalities observed in hypertension are due to associated coronary heart disease or heart failure Exercise may normalize an abnormal tracing or intensify the abnormalities, possibly distinguishing uncomplicated hypertension from that associated with myocardial disease or heart failure Conversion of an abnormal tracing to a normal one after the administration of hypotensive drugs[41] suggests that the ballistocardiographic abnormalities may actually be due to hypertension

Mitral Stenosis

There may be no abnormalities in well compensated cases Or there may be only a diminution in the respiratory variation of the amplitude of I-J More distinctive abnormalities have also been associated with mitral stenosis Davis et al[16] observed an abnormal late diastolic or early systolic footward wave in 13 of 14 patients with pure mitral stenosis This abnormal wave resembled the following footward I wave giving the appearance of a double I wave Occasionally it appeared as if there were a fusion of the waves resulting in a wide rounded I wave The abnormal footward wave in contrast with the normal footward C wave, occurred later than the latter and was associated with a late I wave Despite its consistent occurrence in mitral stenosis this wave is not diagnostically specific for it occurs also in constrictive pericarditis and in aortic or iliac thrombosis The occurrence of the abnormal wave in mitral stenosis was attributed to increased pulmonary vascular resistance right ventricular hypertrophy ventricular asynchrony or an abnormal left atrial ventricular gradient

Henderson[26] observed two abnormal waves in the ballistocardiograms of 100 patients with mitral stenosis (1) an RI footward deflection near the foot of the HI stroke occurring 0 06 to 0 1 second after the beginning of the QRS and (2) an RJ headward deflection immediately after RI and 0 08 to 0 12 second after the onset of the QRS complex of the electrocardiogram These abnormal waves were closely related to the onset of the right ventricular ejection

Mitral Insufficiency

When mitral insufficiency is severe the I wave may be diminished the peak of the J wave may be delayed and it may be slurred or notched A deep M and a tall L and N have been considered as most typical of severe mitral insufficiency but these are not specific These changes have been attributed to exaggerated rapid filling of the left ventricle and reflux in early diastole

Aortic Insufficiency

The I J stroke may be of high amplitude, partly because of augmented stroke volume, but chiefly because of greatly augmented speed of ejection in early systole The peak of the J wave occurs early e g in 0 20 second after onset instead of 0 22 to 0 26 second as occurs normally The K wave may show widening and notching probably due to altered flow in the aorta caused by the aortic reflux

Aortic Stenosis

When the stenosis is severe the I wave may be prominent and widened The widening may be due to delay in impact against the arch due to increased and protracted recoil from ventricular ejection of blood past the narrowed aortic orifice Van Lingen et al[60] described an angulation or bowing of the J-K segment with the low frequency ballistocardiogram With the high frequency apparatus they observed a small K and deep M

Congenital Heart Disease

Pulmonic stenosis may be associated with low amplitude systolic waves and diminution in respiratory variation in amplitude

Atrial and ventricular septal defects and *patent ductus arteriosus* usually show normal ballistocardiograms but the systolic complexes may be of high amplitude

Coarctation of the aorta is characterized by short (cut-off) K waves[7, 37]

Constrictive Pericarditis

There is a reduction in amplitude of the systolic complexes, sometimes associated with an absence of the I wave and notching of the J[65] The L and N waves may be large

Heart Failure

The ballistocardiogram shows abnormalities which may be due to the underlying disease such as coronary heart disease, namely diminution or disappearance of the I wave and decreased amplitude slurring notching and delayed peak of the J wave especially evident in expiration But in addition, in heart failure there are frequently large diastolic waves especially L and N, and there may be a prominent H wave These may be related to exaggerated impacts against the atrioventricular cusps during isometric contraction (H) and isometric relaxation (L), or exaggerated recoil from atrial ejection (N) due to the elevated pressure in the left atrium Low amplitude and distorted configuration of the systolic waves are common in heart failure of the low output type But in the forms of high output failure associated with hyperthyroidism, anemia and so on, the I J waves associated with ventricular ejection may be of high amplitude

CLINICAL EVALUATION

The relative simplicity low cost and ready availability of the portable ballistocardiograph have led to surprisingly rapid acceptance and widespread use of this device in everyday office practice before its physiologic basis has been established, before its clinical value has been clearly demonstrated and its possible field of value sharply defined There is more glibness than experimental basis in the proffered explanations of the mechanism responsible for ballistocardiographic abnormalities observed in various diseases The influence of the surface on which the patient lies, of the ballistocardiographic apparatus, and of extracardiac factors is either insufficiently understood or inadequately stressed The significance of ballistocardiograms which are abnormal when recorded in one direction, but normal in another, is undetermined

It appears that ballistocardiography provides a kind of information regarding cardiac function namely an index of the force of the heart and velocity of ejection, which is different from and may therefore supplement that offered by other graphic methods of examination such as the electrocardiogram From this point of view the ballistocardiograph may be regarded as a research tool that deserves continued exploration On the other hand some investigators regard the ballistocardiogram merely as indicating the degree of elasticity or atheroma of the aorta and hesitate to interpret the ballistocardiogram as a reflection of cardiac output, myocardial strength or coronary disease[11]

Many years of study and correlation may be necessary to determine whether ballistocardiography may be of value as a useful diagnostic or prognostic aid in clinical practice For the present, its general availability renders it simple for the physician or cardiologist to continue to make observations of his own in an effort to correlate them with other better established diagnostic techniques and with clinical progress Until such correlation is unequivocally determined the physician should carefully avoid the danger of rendering a specific diagnosis or prognosis in any individual case based on ballistocardiographic findings or of recommending any specific form of therapy because of such findings

Ballistocardiography may prove to have some statistical merit when applied to large groups of subjects in industrial or insurance medicine,[2, 24] although no conclusive significance may be attached to findings in any individual case Thus it may be found that 1000 individuals at a given age with normal

ballistocardiograms have a much better record of longevity than 1000 individuals of identical age with abnormal ballistocardiograms, yet a similar prognostic conclusion may be erroneous when applied to single persons in either group. Abnormal ballistocardiograms have been noted in the vast majority of patients with angina pectoris, yet it would be improper to conclude that chest pain in a given person represented angina pectoris because his ballistocardiogram was abnormal

In the past the ballistocardiogram has been widely used to measure the stroke output from the amplitude and areas of the I-J stroke[4] [illegible] But although the I-J waves are definitely related to ventricular ejection they are more distinctly determined by the velocity than by the quantity of blood ejected In heart failure the velocity of ejection may be reduced much more strikingly than the quantity while in shock the ejection velocity may be increased although the stroke output is greatly diminished In either circumstance the stroke output determined from the ballistocardiogram will suffer a large error[27]

The ballistocardiogram has also been used to study the effect of various drugs and operative procedures

PHONOCARDIOGRAPHY—HEART SOUNDS

Phonocardiography is the technique of recording the cardiac sounds The phonocardiograph is composed of a stethoscope-like chest piece with a piezoelectric crystal microphone which picks up the vibrations of the heart sounds and transforms them into a varying electrical output according to the stresses imposed by the sound waves The electrical output is then amplified by a stethograph amplifier and finally is recorded by a device incorporated in the electrocardiograph A simultaneous electrocardiogram serves to time the cardiac sounds but for distinguishing special sounds such as a split second sound third heart sound the opening snap of the mitral valve or a gallop sound phlebograms or a carotid artery tracing or electrokymogram may be necessary for correct timing

Stethoscopic and logarithmic phonocardiographs are generally used[90] The *stethoscopic phonocardiograph* records all the sound vibrations brought to the ear when the stethoscope is used audible and inaudible but the very slow vibrations are filtered out The audible vibrations due to cardiac activity are usually those with a frequency of 40 to 100 vibrations per second and under pathologic cardiac conditions up to 1000 per second whereas those below 20 per second are inaudible In the *logarithmic phonocardiograph* the low pitched sounds (low frequency vibrations) which in the ordinary stethoscope arrive at the ear but are not readily perceived are not recorded, only the audible sounds are visually reproduced in this phonocardiogram By means of a distortion yielding a logarithmic type of amplification a record is obtained comparable to the clinical impression of the heart sounds by the human ear with emphasis on the high frequency vibrations

The stethoscopic phonocardiogram not only should be employed for recording the normal heart sounds, but also it is preferred for recording low pitched murmurs such as the apical diastolic rumble of mitral stenosis The logarithmic microphone is preferred for recording high pitched murmurs such as the diastolic murmur of aortic or pulmonary insufficiency In the more modern phonocardiograms such as the Sanborn twin beam and polybeam either stethoscopic or logarithmic records can be obtained with a single microphone, by means of a switch which changes the electrical system The chest piece may be an open bell type which is more efficient for low pitched sounds, or a diaphragm bell which is more effective for high pitched murmurs

There is a third type of microphone, termed a *linear microphone* which records all the chest wall vibrations initiated by cardiac action without distortion In practice this records essentially only the slow vibrations because of their greater amplitude Therefore this microphone is used in cardiography to record chest wall pulsations

Phonocardiography has been of great help in the analysis of the auscultatory findings in the normal and diseased heart [illegible] Phonocardiography may be used to record the fetal heart sounds[8] [illegible] Occasionally it may be needed to distinguish the various sounds of mitral stenosis (to differentiate between a reduplicated second sound the opening snap of the mitral valve or a third heart sound) or to distinguish between a gallop rhythm and reduplicated first heart sound or between a third heart sound and protodiastolic gallop or between a systolic click and an apical murmur

of mitral insufficiency As a rule, however it is not employed with any regularity in the clinical practice of cardiology It is not a substitute for the art of auscultation

For teaching purposes heart sounds have been recorded by a sensitive microphone on phonograph discs which may be readily played back as desired More recently heart sounds have been recorded on tape and played back by tape-recording machines Many advantages accrue from the ability to splice the tape especially the ability to isolate individual heart sounds or murmurs for careful analysis and concentrated audition Recent studies of heart sounds have been made by the method of sound spectrography [56-73] The records disclose the frequency spectrum of the heart sounds as well as their intensity and duration in greater detail than is afforded by conventional phonocardiographs Time is on the abscissa as in the conventional phonocardiogram but the ordinate is frequency, not intensity Intensity is portrayed by the degree of blackness in the recording (Fig 28)

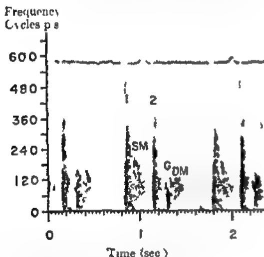


Fig 28 Spectral phonocardiogram Apical recording in patient with rheumatic fever 1 First sound 2 second sound SM systolic murmur DM diastolic murmur G gallop (From McKusick Victor A et al Circulation vol 11 1955)

THE NORMAL HEART SOUNDS[87-90] (Fig 29)

First Heart Sound

The first heart sound occurs early in ventricular systole beginning about 0 02 to 0 04 second after the onset of the QRS complex of the electrocardiogram The main portion of the first sound complex in the phonocardiogram is composed of large irregular fine vibrations with small coarse vibrations preceding and following these The total duration averages 0 14 to 0 15 second, but is briefer in children [88] The first heart sound is due essentially to the sudden tension of the previously lax cusps during closure of the atrioventricular valves [65] Other elements said to contribute to the first heart sound are (1) residual vibrations due to atrial contraction causing the initial vibrations of the first heart sound [66] (2) vibrations due to ventricular muscular contraction, (3) vibrations due to opening of the semilunar valves and vibrations set up by the blood expelled during ventricular systole

The first sound tends to be loud in youth in those with a thin chest wall and in persons with hyperthyroidism mitral stenosis and hypertension Conversely the first sound is apt to be faint in older subjects and in those with pulmonary emphysema pericardial effusion mitral regurgitation shock or severe myocardial disease especially myocardial infarction With complete heart block there is a varying intensity of the first heart sound, depending on the time relations of the atrial and ventricular contractions The first heart sound is usually louder in subjects with a low normal P-R interval than in those with a high normal P R interval These observations suggest that the intensity of the first sound is related to the position of the atrioventricular valves at the onset of isometric contraction or to the speed and consequent impact of their closure which in turn may depend on the speed of the rise in intraventricular pressure in relation to atrial pressure It is presumed that when the ventricles contract very rapidly after the atria the valve cusps are low down in the ventricles and relaxed ventricular contraction then causes them to close with a greater snap and a louder sound When there is a longer interval between atrial and ventricular contraction the cusps have been floated up toward the atrioventricular orifice, are already somewhat tensed when the ventricles contract, and closure of the valve yields a fainter sound

Splitting or reduplication of the first sound may occasionally be heard at the apical region of the heart when there is an exaggeration of the normal asynchronism in the closure of the mitral and tricuspid valves owing to electrical or mechanical factors [75] As



Fig 29 Normal heart sounds Upper tracing phonocardiogram at apex Lower tracing simultaneous electrocardiogram S = first heart sound As = atrial sound of low amplitude inaudible as distinct sound S_2 = second heart sound S_3 = third heart sound A functional systolic murmur inaudible to ear follows the first sound in this phonocardiogram

a rule this is of no clinical significance but may be mis interpreted as a presystolic murmur Splitting of the first sound may be heard in bundle branch block or other conditions in which there is delay in activation of one ventricle relative to another, e g premature ventricular contractions

Second Heart Sound

The second heart sound occurs at the end of systole, its recorded peak coinciding with the end of the T wave of the electrocardiogram or slightly beyond that point It is composed of a large, high pitched diphasic or triphasic wave with small inaudible low pitched vibrations preceding and following the main wave [20, 37] It is produced essentially by the closure of the semilunar valves Low *pitched vibrations due to blood eddies in the* ventricle and the arteries associated with the fall in pressure at the onset of diastole and weak vibrations due to the subsequent opening of the atrioventricular valve may also be recorded with the stethoscopic phonocardiograph The interval between the first and second sounds is briefer than that between the second sound and the *following first sound* because of the usually briefer duration of systole relative to diastole The average duration of the second sound is 0 10 to 0 12 second but below the age of four it averages only 0 06 second

The second sound may be accentuated normally especially in young individuals The intensity of the second sound depends in part on the pressure in the aorta and in the pulmonary artery at the onset of diastole But other factors are important since the pulmonic second sound may be as loud or louder than the aortic when the pressure is lower in the former Perhaps the intensity is more dependent on the relation of the aortic and pulmonary artery pressures to the pressures within their respective ventricles and the speed of the fall in gradient between them Other possible significant factors are the speed and quantity of blood flow the physical state of the semilunar cusps and the ease of transmission of vibrations to the surface of the chest wall depending in part on the position of the aortic and pulmonary valves

The second pulmonic sound is frequently *loud in young healthy persons The aortic* second sound is usually accentuated in systemic hypertension whereas the second pulmonic sound is accentuated and may be louder than the second aortic sound in patients with pulmonary hypertension, especially mitral stenosis in certain congenital cardiovascular lesions in pulmonary congestion *due to left* ventricular failure and in cor pulmonale

A diminution in intensity or absence of the second heart sound may be due to loss of pliability and mobility of the valve cusps or to relatively low pressure in the pulmonic artery Thus the second aortic sound is weak or absent in aortic stenosis and the second pulmonic in pulmonic stenosis

Splitting of the second sound, heard at the base of the heart is due to an asynchronism in closure of the pulmonary and aortic valves [85] It may occur normally in inspiration as a result of the discrepancy in stroke volume of the two ventricles and consequent asynchrony in ventricular contraction and semilunar valve closure The pulmonic sound may be reduplicated in mitral stenosis and the aortic in hypertension Splitting of the second sound may occur more commonly than splitting of the first sound in bundle branch block Splitting of the second sound also occurs in most cases of significant interatrial septal defect, in severe mitral regurgitation, and in respiratory disease resulting in exaggerated cyclic variations in intrapleural pressure [85] Inspiration tends to intensify splitting of the second sound in right bundle branch block and to diminish or eliminate it in cases of left bundle branch block [85]

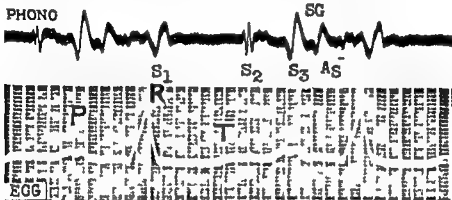


Fig 30 Gallop rhythm Exaggerated S_3 causes diastolic gallop sound Exaggerated A_S causes presystolic gallop sound Their proximity in this case caused a fusion or summation gallop sound (SG) in diastole

Third Heart Sound

The third normal heart sound,[74, 96] usually audible only in children or young adults with a thin chest wall is composed of weak vibrations of low frequency It is best recorded at the apex in the left decubitus position [70] It is produced by the vibrations set up in the ventricles during the rapid inflow phase of early diastole It usually occurs about 0 05 to 0 1 second after the end, or 0 15 to 0 17 second after the beginning of the second heart sound It follows the V wave of the phlebogram but occasionally coincides with it The possible role of the pericardium in the production of a third heart sound has been suggested as a result of study of a case of calcified pericardium [69]

Fourth Heart Sound

An atrial or fourth heart sound[87, 90] is rarely audible under normal circumstances but may be recorded occasionally in the phonocardiograms of children with a thin chest wall or in complete heart block It is believed to be produced by atrial contraction, by the passage of blood through the atrioventricular valves and by the distention of the ventricles by the rapid inflow of blood in mid diastole [98] Atrial sounds are best recorded at the apex, but sometimes may be recorded in the third or fourth left interspace

GALLOP RHYTHM

This refers to a rhythm with an accentuated extra sound besides the two normal sounds, the three sounds creating the auscultatory effect of a canter As a rule gallop rhythm is heard only in the presence of a rapid heart rate

There are three main types of gallop rhythm (1) the protodiastolic, (2) the presystolic and (3) summation gallop In addition there are instances in which an extra sound of uncertain origin occurs during systole This has been termed systolic gallop or systolic click, but its mechanism and significance differ greatly from those of the usual forms of gallop rhythm

It is important to identify the position of the extra sound in order to differentiate the diastolic forms of gallop, which usually denote serious myocardial disease, from the systolic gallop which is of little or no clinical significance When the cardiac rate is very rapid, the "presystolic" gallop sound may become mid diastolic or protodiastolic because

of the shortening of diastole and may thus be indistinguishable from a protodiastolic gallop

Protodiastolic Gallop Rhythm

The extra or gallop sound occurs early in diastole during the phase of rapid filling of the ventricle (Fig 30) It coincides in time with the occurrence of the *third heart sound* i e about 0 16 to 0 2 second after the second heart sound [65] In fact the protodiastolic gallop is most generally believed to represent an accentuated third heart sound[77, 100] and to be due to a similar mechanism [71]

Protodiastolic gallop occurs in left ventricular failure and is believed to result from the very rapid inflow of blood during early diastole into a dilated, flabby left ventricle The sound is caused by the resulting vibrations of the ventricular wall by its impact on the surrounding tissues and chest wall [100] or less likely by vibrations of the mitral valve [81] The high pulmonary venous and left atrial *filling pressure in left heart failure* and acceleration of the heart rate are factors which intensify the phase of rapid ventricular filling and predispose to protodiastolic gallop This type of gallop occurs even with atrial fibrillation since *it is not dependent on atrial contraction*

Protodiastolic gallop rhythm is usually heard best with the patient recumbent and the heart rate accelerated and is located at the apical region in left ventricular dilatation and to the left of the mid or lower sternum in right ventricular dilatation

A distinct third heart sound resembling protodiastolic gallop is heard occasionally in children and young adults But a protodiastolic murmur after the age of thirty is usually due to left ventricular failure or less commonly to right *ventricular failure* Associated evidence of cardiac disease and left ventricular failure supports the interpretation of a gallop rhythm rather than of a normal third heart sound According to Bramwell [64] a *third heart sound, unlike gallop rhythm* is not palpable and may be heard at normal cardiac rates

Presystolic Gallop Rhythm

The gallop sound occurs just prior to the first heart sound preceding it by at least 0 08 sec (Fig 31) It coincides with atrial systole and is believed to represent an accentuated atrial sound [77, 88] The atrial origin of this type of gallop sound is supported by its disap-

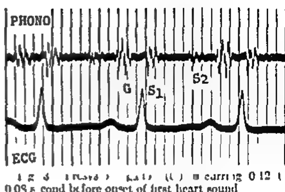


Fig 31 Presystolic gallop (G) occurring 0 12 to 0 08 second before onset of first heart sound

pearance or failure to occur in the presence of atrial fibrillation

When the P R interval is prolonged or when *there is very pronounced tachycardia* the atrial gallop sound is displaced in the shortened diastole and it may be mesodiastolic or protodiastolic The presystolic murmur of mitral stenosis the opening click of the *mitral valve and an audible atrial sound* when there is tachycardia and a prolonged P-R interval may have to be differentiated from gallop rhythm Phonocardiographic tracings are often necessary The Austin Flint murmur *(p 689) has been interpreted as presystolic* gallop rhythm [77]

Summation Gallop (Fig 30)

This is the most common form of gallop rhythm and results from the coincidence of the third heart sound and the atrial sound or of protodiastolic and presystolic gallop sounds Prolongation of the P R interval and pronounced tachycardia are responsible for this coincidence Summation gallop may occur as a result of left or right ventricular failure combined with tachycardia but also occurs in normal persons with tachycardia or in patients *with rheumatic fever* who exhibit tachycardia and a prolonged P R interval

Systolic Click (Gallop) (Fig 32)

The extra or gallop sound has a sharp clicking quality and is heard between the first *and second sounds* [68, 72, 89, 90] *It may be due* to vibrations set up in a dilated aorta or pulmonary artery or to pleuropericardial adhesions or other extracardiac factors [91] The clicks associated with dilatation of a great artery as in essential hypertension or atrial septal defect usually occur early in systole whereas those associated with previous pericarditis and other extracardiac mechanisms usually occur late in systole

THE OPENING SNAP OF MITRAL STENOSIS

This sound occurs very shortly after the second sound and must be distinguished from a reduplicated second sound, from the physiologic third heart sound and from gallop

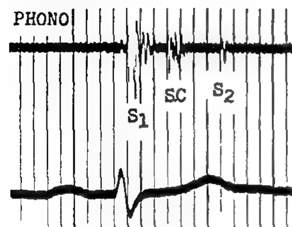


Fig 32 Systolic click (S C) also termed systolic gallop in a 53 year old man with pleuropericardial adhesions

rhythm For details and differentiation see p 659 The phonocardiogram in conjunction with a simultaneous jugular venous pulse tracing or apex cardiogram is important in this differentiation (Fig 33)

CARDIAC MURMURS

Cardiac murmurs are represented on the phonocardiogram usually as a series of vibrations of varied pitches So-called musical or sea gull murmurs (p 688) are recorded as a series of regular vibrations of the same frequency

Systolic Murmurs

Systolic murmurs may be revealed as vibrations merely prolonging the first sound or they may be much more distinct and of greater intensity Leatham[79] classifies systolic murmurs as (1) ejection murmurs (aortic stenosis, pulmonic stenosis), which occur predominantly in midsystole, and (2) regurgitant murmurs (mitral and tricuspid insufficiency) in which the murmur occurs usually throughout systole (pansystolic) The apical systolic murmur of mitral regurgitation is usually a decrescendo murmur with greater vibrations at first diminishing in intensity and ending long before the second sound The vibrations are of varied pitch chiefly of high frequency Occasionally the murmur is composed of high frequency vibrations and lasts throughout most of systole Phonocardiography is no more helpful than auscultation in determining whether there is a significant mitral regurgitation in patients with mitral stenosis who are being considered for mitral commissurotomy

The systolic murmur of aortic stenosis is often recorded as a diamond shaped series of vibrations beginning after the first sound at the aortic area, increasing in amplitude toward the middle of systole diminishing again thereafter and ending before the onset of the second sound which may be absent This distinctive pattern when recorded at the apex may serve to distinguish from mitral regurgitation those occasional cases of aortic stenosis with a murmur heard only or best at

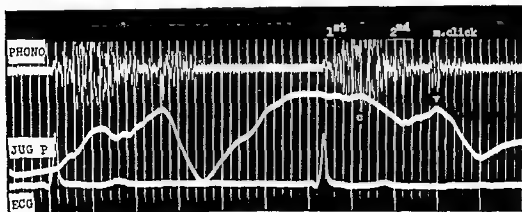


Fig 33 Opening snap (apical area) in a case of mitral stenosis Note occurrence of opening snap or mitral click (m click) at peak of V wave of jugular venous pulse tracing Systolic and diastolic murmurs follow first sound and second sound respectively

the apex of the heart. There may also be a loud series of systolic vibration lasting through all of systole and heard in the second left or second right interspace in cases of aortic or pulmonic stenosis. Pulmonic systolic murmurs in apparently normal children are recorded as a simple wave of measurable frequency with sporadic distortions.[illegible] *Musical murmurs* may have a concertina like pattern on the phonocardiogram with increasing and diminishing intensity of vibrations but with frequencies which are identical or only slightly varied. These murmurs may be noted in cases of myocardial infarction and calcific aortic stenosis and following rupture of a valvular cusp or a papillary muscle.

Apical Diastolic Murmurs

Apical diastolic murmurs indicative of mitral stenosis are shown by phonocardiograms to consist essentially of low frequency vibrations, which account for their rumble quality (Fig 33). The murmur may begin early in diastole, continue into mid-diastole and even merge with the increased vibrations of a presystolic murmur. Or the rumble may be limited to early diastole or to mid diastole—most often the latter. There may be only the low pitched vibrations with increasing intensity and merging into the first sound which represent the typical crescendo murmur of mitral stenosis. However phonocardiograms have shown that the vibrations producing this murmur may diminish before the following first sound and that the crescendo effect is present because of the sharp first sound terminating a diminishing murmur. The phonocardiogram may be useful in distinguishing this presystolic murmur by its time relationship with a simultaneous electrocardiogram from so-called pseudo-presystolic murmurs which are really modified first sounds simulating murmurs[62] and which are apt to be heard in cases of hyperthyroidism and an overacting heart. When the murmur of mitral stenosis is limited to a very small area near the cardiac apex and when it is audible only with acceleration of the cardiac rate and with the patient in the left lateral position the phonocardiogram may be no more perceptive than the ear unless these conditions are satisfied and the bell of the phonocardiograph is properly placed.

The phonocardiograph has not demonstrated any clear difference between the presystolic murmur of mitral stenosis and the Austin Flint apical presystolic murmur of aortic regurgitation.[67] However, a distinction may be made by other features of the tracing including the opening mitral snap and the character of the first sound at the apex and the second sound over the pulmonic area.

Basal Diastolic Murmurs

Diastolic murmurs at the base, due to aortic or pulmonic insufficiency, show high frequency vibrations of low or moderate intensity which begin early in diastole and diminish in intensity usually terminating in mid-diastole.[illegible] Louder and more prolonged murmurs are apt to occur with syphilitic bacterial endocarditic dissecting aneurysmal and traumatic forms of aortic regurgitation than with the rheumatic form. Occasionally a sea gull cry type of aortic diastolic murmur is heard in syphilitic aortic insufficiency with everted aortic valve but also in the aortic insufficiency associated with bacterial endocarditis or trauma. (See Chapter 27.) In these the murmur is represented by regular vibrations of uniform frequency.[75] The phonocardiogram does not differentiate the murmur of pulmonic from that of aortic insufficiency.

Continuous Murmurs

Continuous murmurs often described as machinery like humming top wind mill or tunnel murmurs found in patent ductus arteriosus arteriovenous fistulas and rupture of a syphilitic aortic aneurysm into the pulmonary artery are represented by large vibrations varying often in intensity and frequency and extending throughout systole and diastole. The vibrations usually increase in intensity at the end of systole mask the second sound and diminish in diastole.

Pericardial friction rubs are recorded as vibrations of varied pitch but usually of high pitch during systole and diastole (Fig 34).

THE JUGULAR VEIN TRACING (VENOUS PULSE)

Although the electrocardiogram has almost entirely eliminated the clinical use of the jugular vein tracing (phlebogram) the latter is still important in timing certain events in the cardiac cycle and may be of aid in diagnosing cases of organic and functional tricuspid insufficiency or tricuspid stenosis and certain arrhythmias especially when the P wave in the electrocardiogram is obscured.[106, 105, 11]

With the subject in the supine position or semirecumbent if he is orthopneic, a special applicator in the form of a double-rim circular cup is applied to the right jugular bulb, where it is held to the skin by suction created in the outer chamber of the cup[107] The inner chamber picks up the venous pulsations, which transmit pressure changes to a crystal type, linear microphone which in turn converts them into electrical waves The latter pass through an amplifier and are then recorded with the aid of a camera The patient should hold his breath during the recording least in part to transmission of the underlying carotid pulse or to transmission of the pulse of the ascending aorta or arch of the aorta to the superior vena cava and thereby to the jugular vein The beginning of the upstroke of the "c" wave falls about 0 14 second later than the onset of the QRS in an electrocardiogram taken simultaneously

The *third positive wave the "v" wave* or "early diastolic wave" mirrors the rise in volume and pressure in the right atrium as it fills at the end of systole and the early part of diastole just before the tricuspid valve opens

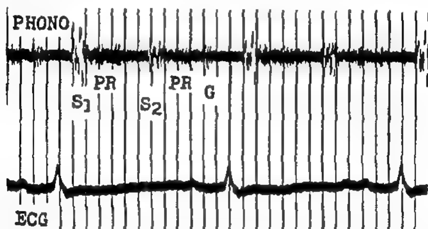


Fig 34 Pericardial rub (PR) in systole and early diastole associated with presystolic gallop (G)

The Normal Jugular Venous Pulse (Fig 35)

Normally there are three positive waves in the jugular venous pulse tracing[108, 104, 101] These pulsations are determined essentially by pressure and volume changes in the right atrium which are reflected by corresponding alterations in the jugular vein

The *first or "a" wave* occurs shortly before the apical impulse and is due to right atrial contraction It is absent in atrial fibrillation It is exaggerated with simultaneous contraction of the atria and ventricles which causes regurgitation of blood into the venous system as in heart block nodal rhythm or nodal premature beats It is also prominent in tricuspid stenosis with regular sinus rhythm and in tricuspid insufficiency In cases of interatrial septal defect there is a double A wave due to the left-to right shunt as well as to atrial contraction[10]

The *second or "c" wave*[109] or "systolic wave" is a slight peak due to elevation and closure of the tricuspid valve at the onset of ventricular systole but it has also been attributed, at

The "v" wave is also called the stasis wave and is especially exaggerated in cases of right heart failure The downward limb of the "v" wave represents the fall in atrial and venous pressure as the tricuspid valve opens

Between the positive "c" and "v" wave peaks i e throughout most of ventricular systole the jugular vein empties almost completely into the superior vena cava and right atrium and venous tracings show a pronounced depression or negative wave termed "x" (systolic collapse) Because this venous collapse is the most striking feature of the normal venous pulse, the latter is termed a *negative venous pulse* The "x" depression in systole is due to the aspirating effect on the blood in the veins when blood is expelled from the thoracic cavity and the tricuspid valve and atrioventricular septum are drawn down in systole When the right atrial pressure is elevated in right heart failure and especially in tricuspid regurgitation the "x" descent is greatly diminished or is replaced by a positive wave (positive venous pulse) (See

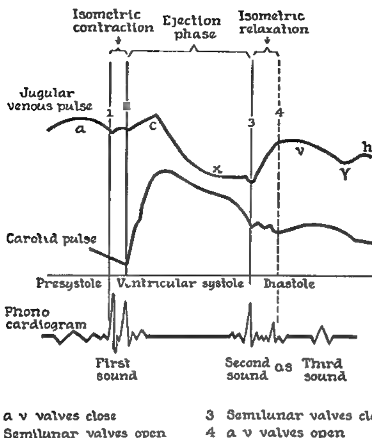


Fig 35 Relation of waves in jugular venous pulse tracing to events in cardiac cycle as seen in carotid pulse tracing and phonocardiogram

Chapter 29) Following the "v" wave there is a negative depression ("y" wave, diastolic collapse) This represents the emptying and fall in pressure in the right atrium after the tricuspid valve opens and before atrial contraction Following the "y" there may be another small positive wave, the "h" wave attributed to floating up of the tricuspid valve prior to atrial contraction

HEPATIC PULSE TRACING

The hepatic pulse tracing is essentially like that of the jugular venous pulse but the "c" wave seen in the jugular venous pulse tracing is virtually absent in the hepatic pulse tracing A cup attached to a linear microphone is applied to the right hypochondrium if the liver is enlarged, or on the right side of the epigastrium in normal persons and held in place by a rubber strap

Normal Hepatic Pulse[108, 111]

The normal hepatic pulse tracing shows a presystolic "a" wave occurring during atrial contraction and virtually simultaneous with the "a" wave of the jugular pulse This is followed by a deep negative wave ("x") representing systolic collapse as the liver empties into the inferior vena cava and right atrium during ventricular systole The systolic collapse is followed by a "v" wave representing the increase in hepatic volume until at the peak of the "v" wave the tricuspid valve opens The descending limb of the "v" leads to another negative wave the diastolic collapse ("y") The major waves "a" and "v" of the liver pulse are recorded approximately 0 02 and 0 04 second later than their corresponding waves in the phlebogram In addition to these major waves there may be smaller notches due to transmitted impulses from the heart through the diaphragm A small positive notch may occur in early systole

Positive (Systolic) Liver Pulse

A prominent positive wave during systole instead of the normal systolic collapse (negative wave) occurs in a variety of conditions

in which a rise in right atrial pressure during ventricular contraction is transmitted as a pulse to the inferior vena cava and liver Most frequently, a positive systolic wave is observed in functional or organic tricuspid insufficiency (p 714) Thus it is noted especially with rheumatic mitral stenosis and in coronary heart disease when these are complicated by advanced right heart failure I have observed it in cases of cor pulmonale and severe right heart failure and in cases of congenital heart disease Rarely in nodal rhythm atrial contraction simultaneous with ventricular contraction produces a positive liver pulse The positive liver pulse is associated with a palpable systolic pulsation or expansion of the liver

Presystolic Liver Pulse (See also p 715)

In cases of tricuspid stenosis, usually associated with severe mitral stenosis and also in other conditions[110, 103] (p 715) the rise in right atrial pressure during atrial systole is transmitted to the hepatic inferior vena cava and hepatic veins and may give rise to an extremely exaggerated a wave and a palpable presystolic liver pulsation Usually however tricuspid insufficiency is associated with the tricuspid stenosis and the systolic pulse of the former dominates the liver pulse tracing and obscures the presystolic pulse When atrial fibrillation is present there is no presystolic 'a wave or pulse (see also p 715)

CARDIAC CATHETERIZATION—TRACINGS OF INTRACARDIAC AND INTRA VASCULAR PRESSURE

The procedure of cardiac catheterization[1, 9, 116, 1 5, 120, 118] is included here because graphic methods are used to record the pressures in the various cardiac chambers and great vessels Actually the technique serves to record pressures to determine the oxygen content, to discover an abnormal passage which the catheter may enter and more recently to introduce contrast material for selective visualization of specific portions of the heart or great vessels Cardiac catheterization has been widely used to make physiologic observations which have had many important clinical applications, particularly in congenital heart disease mitral stenosis cor pulmonale and during pregnancy (*For details as to the role of* cardiac catheterization in individual diseases and appropriate bibliography see sections on specific diseases)

RIGHT HEART CATHETERIZATION

Indications

Since to a large extent right heart catheterization *is still a research tool*, it is indicated *and performed in order to obtain further* physiologic observations and to correlate these with clinical data From the clinical viewpoint it is indicated whenever required to establish a definite specific diagnosis This has become increasingly important as cardiac lesions have become amenable to surgical correction, by confirming or excluding a tentative diagnosis catheterization has served to confirm the desirability of a surgical procedure or to prevent an unjustifiable thoracotomy

The widest clinical application has been in congenital heart disease especially for the diagnosis of atrial and ventricular septal lesions, pulmonic stenosis and patent ductus arteriosus without the typical murmur Catheterization has been particularly useful with infants and very young children in whom the diagnosis of congenital cardiac lesions by physical diagnosis conventional x ray study and electrocardiography is notably difficult It has been used with increasing frequency recently in cases of mitral stenosis and other acquired valvular defects chiefly to study the circulatory dynamics and to follow the pathologic physiology during the natural history of the lesion and after commissurotomy Such studies have also indicated a possible practical clinical application they may aid in determining the type of case likely to benefit from this surgical procedure namely the patient with pulmonary artery hypertension and a high atrioventricular gradient

Preparation and Premedication of the Patient

The procedure its need and the minimal risk involved are explained in general terms to the adult patient or to the parent of a child Permission is obtained in writing When possible and desirable the patient is brought to the catheterization laboratory on the day preceding the procedure in order to familiarize *him with the staff the surroundings and the* equipment When the respirometer or the bicycle ergometer is to be used for physiologic studies, the patient is instructed in its use *and permitted trial performances until he* breathes evenly at rest and during exercise on the bicycle ergometer

The evening before catheterization the pa

tient is given 600 000 units of aqueous procaine penicillin intramuscularly (proportionally less for infants and young children and this dose is repeated thereafter every 12 hours for four days after the procedure Breakfast is withheld on the morning of catheterization and 0 1 gm of Nembutal is administered orally one hour before catheterization

General anesthesia by means of rectal Avertin and subcutaneous atropine followed by an intravenous drip of Pentothal sodium has been found necessary in infants and young children in order to assure cooperation and maintenance of the steady state However some groups of workers premedicate children up to the age of eight years with morphine sulfate 1 mg (1/64 grain) per 10 pounds of body weight and sodium phenobarbital 30 mg (½ grain) per 10 pounds of body weight one-half to one hour before the procedure and only occasionally supplement this during catheterization by Seconal intravenously 0 5 to 1 0 mg per pound of body weight [19]

The patient is brought to the laboratory by wheel chair or stretcher and is examined to exclude any complication especially an intercurrent infection or an intensification of heart failure

Technique[17 18]

Catheterization is performed by a team of several physicians a nurse and one or more technicians to analyze blood samples and samples of expired air One physician performs the actual insertion and manipulation of the catheter and withdrawal of blood samples from the catheter a second performs the fluoroscopy to control the position of the catheter during its various manipulations inserts the indwelling arterial needle and withdraws samples from it and also supervises the use of the respirometer while a third physician handles the apparatus by which he records pressures from the catheter and arterial needle observes the electrocardiographic record on the oscilloscopic screen and reports the occurrence of any arrhythmia or other abnormality

The pressure recording apparatus is set up and calibrated It consists of Statham gauge transducers with a four channel oscilloscopic recorder The manometers are connected through fluid filled tubing at the proper levels to a three way stopcock attached to the proximal end of the catheter and to the indwelling arterial needle An optical system transmits the pressure deflections to a camera which records the pressures on film moving with a speed of 50 to 75 mm per second A simultaneous electrocardiographic tracing may be made

The patient lies supine on the fluoroscopic table which is covered by a pad or sponge rubber mattress The operator wears a lead apron and scrubs and dons sterile gown and gloves as for a surgical procedure Following local 2 per cent procaine anesthesia a percutaneous puncture of the brachial artery is made with a special No 22 or No 20 indwelling arterial needle (Becton Dickinson and Co Rutherford N J) to which a three way stopcock is attached It is left in place and kept patent with a constant drip of dilute aqueous heparin in a solution of 5 per cent dextrose in distilled water Blood samples and pressure readings are made by appropriate turns of the stopcock

An antecubital vein is selected in adults or older children the right or left saphenous vein in infants and young children and the field is sterilized with Merthiolate and properly draped with sterile sheet and towels A cut down is performed under 2 per cent procaine anesthesia if no general anesthetic has been administered the vein is isolated ligated and incised proximal to the ligature A No 6F or 7F flexible radio-opaque catheter made of nylon with unwettable plastic covering 100 cm long with a curvature near the entering tip a hole at the tip and an adapter for a three way stopcock at the outer end (supplied by U S Catheter and Instrument Co Glens Falls N Y) is autoclaved at least some hours before use The catheter is inserted through the incision in the vein and advanced under fluoroscopic control into the superior vena cava and progressively into the pulmonary artery or its smallest ramification for pulmonary capillary pressure measurement If obstruction is encountered at any point further progress is made by rotation of the catheter and by slight withdrawal and advancing the catheter again Spot x ray films are taken to verify the position of the catheter when there is uncertainty as to its location or when it enters an abnormal vessel or chamber

Patency of the catheter is maintained by a constant drip as described for the indwelling arterial needle Fluoroscopy is carefully timed and limited preferably to less than ten

minutes, with an absolute maximum of twelve minutes.

The tip of the catheter is led along the walls of the pulmonary artery, the right ventricle and the right atrium during its stay in these regions. One may thus determine whether there is a stenosis of the pulmonary valve or conus (infundibular stenosis) or whether the catheter passes through a patent ductus arteriosus into the aorta. When the catheter is in the right ventricle the size of this chamber can be assessed. The aorta may be entered in tetralogy of Fallot or dextraposition of the aorta. In the right atrium one may enter an atrial septal defect or a pulmonary vein which empties into the right atrium. The catheter may also be passed into the coronary, hepatic or renal veins and their content of blood gases and other substances determined to study the metabolism of the heart, liver or kidney respectively.

Blood samples from the catheter and pressure recordings are not taken until the catheter has been advanced to the farthest point desired, otherwise further introduction of the catheter may be prevented by venospasm before passage has been completed. However, if in its initial passage the catheter is introduced into a pulmonary vein, left atrium or ventricle or aorta, blood samples and pressures are immediately taken from these locations. Furthermore, reports of abnormal changes in pressure or of gas analyses made during the procedure may indicate the desirability of repeated determinations or tracings or a change in routine procedure. As the catheter is withdrawn, samples of blood are aspirated and pressures recorded from each successive vessel and chamber including the pulmonary artery and branches, outflow tract of the right ventricle, midportion or apex of right ventricle, tricuspid area of right ventricle, tricuspid area of right atrium, mid right atrium, superior vena cava and inferior vena cava near the right atrium. Arterial blood samples and pressure recordings are taken simultaneously from the indwelling arterial needle.[2]

The oxygen and carbon dioxide content of the blood is determined by the method of Van Slyke and Neill (Chapter 10). The blood samples are carefully drawn from catheter and arterial needle by a Luer Lok syringe with great care to avoid air bubbles from entering the circuit or the syringe. After rotation of the blood in the syringe, it is transferred to Ostward Van Slyke pipettes under airtight conditions and the determinations carried out promptly. If desired, the syringes with blood samples are stored in ice for later determinations. The oxygen content is determined and then the oxygen capacity. Oxygen saturation is calculated by dividing content by capacity.

The oxygen consumption is determined by the closed method using a modified standard metabolism apparatus such as the Collins respirometer or preferably by the open method in which samples of expired air are collected by facial mask or mouthpiece and nose clip into a Douglas bag or Tissot spirometer and analyzed for their gaseous content (Chapter 39).

At the end of the procedure the catheter is withdrawn slowly by steady tension, the ligature on the antecubital vein is removed, bleeding controlled by pressure, the skin incision closed by flamed adhesive and a sterile dressing applied. If the saphenous vein was used, it is tied near its junction with the femoral vein and the skin sutured. The arterial needle is withdrawn and hemostasis effected by immediate pressure for at least five minutes.

Complications

There is surprisingly little risk in the procedure of cardiac catheterization, especially when one considers that the subjects are usually seriously ill cardiac patients. There were 4 fatalities among 5700 instances of right heart catheterization.[1, 4] Great care should be taken to avoid air embolism, especially in patients with right to left cardiac shunts, but despite this potential danger, air embolism has been a great rarity. Pulmonary thrombosis may occur.[139]

Cardiac arrhythmias are the commonest complications of cardiac catheterization, chiefly premature beats but rarely paroxysms of supraventricular tachycardia, runs of ventricular tachycardia, atrial fibrillation and right bundle branch block.[138, 130] The extrasystoles are particularly likely to occur when the catheter passes through the tricuspid valve or contacts the ventricular septum near the outflow tract, or if excessive suction is produced in taking samples of blood from the right ventricle.

Venous thrombosis and possibly, rarely, cardiac endocardial thrombosis occasional

chills and rare instances of pulmonary edema are other complications which have been noted. In young children or infants the amount of blood withdrawn for gas determinations may be large enough to justify blood replacement.

CATHETERIZATION OF THE LEFT HEART AND AORTA

The left side of the heart has been catheterized by introduction of a catheter into the radial artery or brachial artery[130, 136, 137] and retrograde passage of the catheter up the arch of the aorta past the aortic valve and into the left ventricle. The procedure has been associated with various complications including *rupture of the aorta or of an aortic leaflet*, occlusion of a coronary artery and ventricular tachycardia and ventricular fibrillation. Retrograde passage of the catheter via the brachial artery to the aorta only without passing the aortic valve avoids most of the risk and has been used to make direct recordings of the aortic pressure pulses, especially in coarctation of the aorta, aortic insufficiency and hypertension.[138] Catheters have been introduced into the radial or brachial artery and left common carotid artery and contrast material injected for thoracic aortography[1, 3] (p. 17).

Direct simultaneous pressure readings from the left side of the heart may be made and recorded at the time of a cardiac operation by means of a needle inserted into the left atrium, left ventricle and aorta.[1, 1] By introducing a double lumen catheter whose orifices are 10 cm apart so that one lumen is in the left ventricular and the other in the left atrial cavity, simultaneous pressure determinations can be made from these chambers and the pressure differences (gradient) instantaneously derived by electrical subtraction.[1] A variety of other approaches have been made to measure and record the pressures in the left side of the heart and aorta without operation by direct puncture through the chest[115, 112, 136, 1, 35, 145a] or by bronchoscopy[113] (Chap. 26). Goldberg et al.[13] recorded pressures from all chambers of the heart and determined the cardiac output and pertinent gradients in cases of mitral stenosis and of aortic stenosis by simultaneous catheterization of the right heart through a peripheral vein and the left heart by a 6-inch No. 18 needle introduced into the left atrium paravertebrally and followed by a catheter passed through the needle into the left atrium, left ventricle and aorta. A somewhat similar technique was employed by Blakemore et al.[119] to determine the pressure gradient across the mitral or aortic valves as a basis for assessing the degree of stenosis and *selecting patients for appropriate cardiac surgery*. Wood et al.[143] modified available procedures to allow simultaneous measurements of aortic, left ventricular and left atrial pressures along with the blood flow (cardiac output). For accurate interpretation of the pressure gradient across a stenotic valve, the flow across the valve was measured simultaneously with the pressure gradient.

NORMAL PRESSURES IN THE CARDIAC CHAMBERS AND PULMONARY ARTERY

The normal pressures obtained by cardiac catheterization are shown in the table below (see also Fowler et al.[131], Braunwald et al.[1, 1]).

OTHER GRAPHIC METHODS

A variety of other graphic methods have on occasion been employed but have not attained significant clinical usefulness. A few which have been discussed in recent years may be mentioned so that the interested reader may refer to the original reports.

CARDIOGRAPHY—KINETOCARDIOGRAPHY

Cardiac sounds and especially cardiac murmurs are associated with vibrations of the chest wall which are of relatively high frequency. In addition cardiac activity produces so-called slow vibrations of the chest

NORMAL INTRACARDIAC PRESSURES

	SYSTOLIC mm Hg	DIASTOLIC mm Hg	MEAN mm Hg
Right atrium	4 to 6 (5)	−2 to +2 (1)	2 to 4 (avg 3)
Right ventricle	20 to 30 (25)	0 to 4	
Pulmonary artery	20 to 30 (25)	7 to 12 (9)	13 to 18 (avg 15)
Pulmonary capillary			4 to 12 (avg 8)
Left atrium			4 to 8 (avg 6)
Left ventricle		3 to 10 (6)	

wall, which, unlike the vibrations of most cardiac sounds and murmurs, are as a rule readily visible and palpable The slow chest wall vibrations include the apical impulse and other precordial movements which may become especially prominent in cardiac disease

Various devices have recently been employed to record the e vibrations or pulsations over the apical, pulmonic aortic and tricuspid regions and over the epigastrium Johnston and Overy[136] used an electromanometer connected by short hard rubber tubing with a funnel pickup device applied airtight against the chest wall Luisada and Magri[138] employed a linear (crystal) microphone attached by its cable to the electrocardiograph for recording The vibrations of the chest wall are transmitted to the air in a funnel chest piece and thence to the linear microphone, which transforms the air waves into electrical pulsations These are recorded as a continuous tracing by the electrocardiograph s galvanometer Eddleman and associates[1 8] used as their pickup device a sensitive metal bellows with a small metal arm whose end piece is flat and applied airtight to the chest wall The vibrations of the latter are transformed by the bellows in an airtight system into a pulse wave which, in turn, is converted by a piezoelectric transducer into an electric current recorded by an electrocardiograph

The normal pattern of the precordial cardiogram or kinetocardiogram and its variants have been described and distinctly different patterns have been observed in patients with organic heart disease The significance of these differences is uncertain and the method has no clinical importance at the present time

RADIOCARDIOGRAPHY

This is a technique of recording the concentration of intravenously injected radioisotope in the cardiac chambers A Geiger Muller counter is placed over the precordium and the varying number of counts is recorded as a curve by an ink recording device or electrocardiograph Prinzmetal et al[u] injected 10 to 20 millicuries of radiosodium with a half life of 14 to 18 hours while Luisada and associates[137] used 50 microcuries of di iodo fluorescein which has a half life of seven days Shipley et al[145] employed a scintillation counter, which permits the use of very low doses (4 microcuries) of I^{131} albumin to record the radiocardiogram

Within two seconds after the injection, there is a sharp upward wave (R) lasting 3 or 4 seconds, due to the arrival of radioisotope in the right heart chambers This is followed shortly by a second, lower, rounded wave (L) starting 5 to 7 seconds after the injection and lasting about 5 or 8 seconds and due to radioisotope in the left cardiac chamber When the drug has left the heart, the curve returns to the baseline The time of arrival of the radioisotope in the right and left sides of the heart denotes the circulation time, and the concentration is an indirect measure of the residual cardiac blood volume Changes in the curve occur in heart failure, congenital cardiac shunts[134] constrictive pericarditis and vascular obstructions In mild heart failure there is a widening of the interval between the two hump-like waves of the radiocardiogram[145]

RHEOCARDIOGRAPHY[135 141]

During the course of the cardiac cycle the opposition or total resistance to the flow of an alternating current sent through the body i e, the body impedance undergoes rhythmic variation If two electrodes of a high frequency circuit are applied to the body, fluctuations in electrical impedance in the course of the cardiac cycle may be measured and recorded on the electrocardiograph The resulting curve has been termed a rheocardiogram In a recently employed method the body is connected to a generator of high oscillation frequency (14 000 cycles per second) and receives about 20 milliamperes current While the body and series resistor is placed in one branch of the circuit the other branch contains a Wheatstone bridge which measures the impedance between a pair of electrodes placed in the apical region of the heart and at the right shoulder A change in impedance affects the balance of the bridge and the varying bridge voltage is amplified and recorded as a curve by the electrocardiograph

This and similar techniques of measuring rhythmic changes in body impedance (rheocardiography) have also been termed di electrography[114 148] and impedance plethysmography[140] and unfortunately, radiocardiography the latter is not be be confused with the method of radiocardiography described above

The factors re ponsible for the rhythmic change in body impedance are uncertain. They were first attributed to changes in cardiac volume during the cardiac cycle and the rheocardiogram was interpreted as a volume curve of the heart during its various pha es of activity and relaxation. More recent studies indicate that the changes in body impedance are related to rhythmic changes in the caliber or blood content of the body vessels during the cardiac cycle[160, 1 0]. Rheocardiography is of no demonstrated clinical value at the present time.

Dye Dilution Curves have been u ed to local ize cardiovalvular defects[153] (p 666) and de termine the presence of shunts in congenital heart disease[151, 152] (p 798)

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PART II

CIRCULATORY FAILURE

Chapter 4

CARDIAC FUNCTION AND CARDIAC FAILURE

DEFINITION

The function of the heart is to maintain an adequate output of blood at all times. Cardiac failure denotes that the output of the heart is insufficient for the needs of the tissues. Thus a normal cardiac output is not a fixed absolute value but must be assessed in terms of variable tissue requirement.

The failing heart may supply an adequate flow of blood when a patient is at rest but not under the stress of exercise, of pregnancy, of fever and infection or of hyperthyroidism. Under certain circumstances, e.g., severe anemia, the cardiac output of the patient at rest may even exceed that of normal individuals.[illegible] [10] Heart failure may be present despite this augmented cardiac output if the latter does not quite compensate for the deficiency in oxygen content of the blood, i.e., if the tissues do not receive their needed supply of oxygen despite an increased blood flow. The adequacy of cardiac function must therefore be defined not only in terms of cardiac output but also in terms of its capacity for performance under various loads.

The definition of cardiac failure in terms of an inadequate cardiac output refers to a deficiency on the arterial side of the circulation. When heart failure is defined in terms of the venous side of the circulation, it denotes an inability of one or more chambers of the heart to accept and expel the venous return throughout the range of physiologic activity. Finally, as we shall see, neither of these definitions is suitable in clinical practice at the bedside. Then cardiac failure is best defined as a clinical syndrome characterized by distinctive symptoms and signs which are the consequences of the above-mentioned disturbances in cardiac output and in cardiac disposition of the venous return.

THE LAW OF THE HEART

Cardiac Response to Increased Venous Inflow

In a controlled circulation, such as the heart lung preparation, the arterial resistance (resistance to outflow) can be kept constant by a clamp on the aorta and the rate of the heart may be maintained constant by an excitatory stimulus whose rate is fixed. The inflow into the heart can be varied by infusions into the external jugular vein and the effects studied by observing the cardiac output, the size of the cardiac chambers and the intracardiac pressure curves.

Patterson and Starling[54] observed that when the venous inflow was increased the intra-atrial and ventricular pressures rose. There was an increase in the diastolic size of the heart due to inability to eject immediately the increased amount of fluid. With the next few heart beats there was a progressive increase in cardiac output until this was equal to the increased inflow and equilibrium was restored. Up to a certain physiologic limit further increase in cardiac inflow resulted in continued increase in diastolic cardiac volume and this, in turn, in an augmented cardiac output.[54] [illegible] In this way the heart was able to adapt itself to respond adequately to an increased inflow of several hundred per cent. When the heart began to fatigue, an augmented inflow caused an enlarged diastolic volume without a concomitant rise in cardiac output and the heart no longer ejected as much blood as it received. This deficiency was denoted by a rise in venous pressure as well as by dilatation of the heart.

Cardiac Response to Increased Aortic Resistance

In similar experiments the venous inflow was maintained constant while the aortic resistance to outflow was increased by tightening the clamp on the aorta. In the subsequent

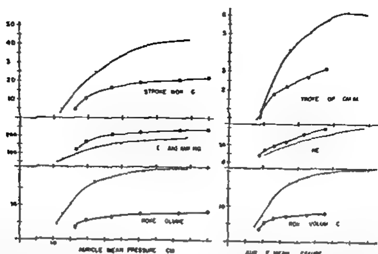


Fig 36 Simultaneously obtained left and right ventricular function curves (Starling curves) in the dog s heart before and during increased aortic resistance Dots indicate control curves Circles indicate curves when screw-clamp increased aortic resistance (From Sarnoff S J and Berglund E Circulation vol 9 1954)

cardiac contraction the left ventricle ejected less blood than formerly (i e less than it received) The remainder was added to the constant venous inflow in diastole The diastolic volume was thus increased Pressure curves of the left ventricle showed an elevation of initial tension and there was an increased force of contraction The heart s output became larger until it ejected as much blood as it received (i e the output returned to its original level) and equilibrium was restored The cardiac output could be thus maintained even when the arterial resistance (pressure) was more than doubled

Thus either an increased venous inflow or an increased resistance to cardiac outflow results first in an increased intracardiac tension and *volume in diastole and then in an increased* force of contraction [53, 54] Consequently despite the greater work imposed by these factors the heart either increases or maintains its output Studies of the respiratory metabolism of the heart revealed that the increased force of contraction following enlargement of the diastolic volume was associated with the liberation of greater chemical as well as mechanical energy [15, 60] *The observation that within physiologic limits a larger diastolic cardiac volume results in a greater energy of contraction and a greater amount of chemical change at each contraction has been termed the Law of the Heart (Starling)* [59] It is the fundamental principle governing the adaptability of the heart in coping with an increased venous inflow of blood to the heart or an increased resistance to its outflow Its validity in the presence of an intact circulation has been both questioned[4, 6, 57] and extended [55]

Starling Curves

However with increasing inflow and increasing diastolic volume the crest of augmented cardiac output is reached and passed Further increments in venous return overload the heart and diminish the cardiac output As the physiologic fitness of the heart muscle is impaired the point of overloading is reached earlier i e with smaller quantities of venous return The reduction in cardiac output relative to filling pressure with greatly increased venous inflow is commonly designated as the descending limb of the Starling curve *Recent studies in the dog with continuous registration of cardiac output and atrial and arterial pressures have confirmed the occurrence of a descending limb when myocardial function is compromised but not in the normal heart with intact pericardium [55] Furthermore it has been suggested that there is not one but a family of Starling curves for a given heart indicating differences in ventricular performance when certain work conditions are altered e g a change in myocardial contractility coronary artery constriction or increased aortic resistance[55] (Fig 36) It has been found that hemodynamic factors such as work load and heart rate affect the mechanical properties of the ventricle[10b, 53] and its oxygen consumption [10a]

Oxygen Consumption and Mechanical Efficiency

The respiratory metabolism of the heart has also been studied in vivo by the technique of catheterization of the coronary sinus. The coronary blood flow which drains into the coronary sinus is estimated by a modification of the nitrous oxide method for measuring cerebral blood flow[11, 5] The oxygen consumption is determined from this value and from simultaneous measurements of the oxygen concentration of coronary sinus blood and of blood from any systemic artery. Since coronary sinus blood does not represent true coronary mixed venous blood but essentially (although perhaps not entirely or exclusively) blood draining the left ventricle the calculated oxygen consumption is relatively accurate only when computed in terms of 100 gm of left ventricular muscle. For total left ventricular oxygen consumption it is necessary to estimate left ventricular weight. While calculations of left ventricular weight may be reasonably accurate in non hypertrophied hearts such calculations in hypertrophied hearts are subject to great error.

The data on myocardial oxygen consumption in vivo obtained by this method have been interpreted as not conforming with the Law of the Heart which is based on observations with the heart lung preparation[7] Left ventricular hypertrophy without failure was found to be associated with a normal oxygen consumption per 100 gm of muscle although increased oxygen consumption might be anticipated from the Law of the Heart. However the latter clearly refers to an increased oxygen consumption with increased diastolic volume only if the physical fitness of the fiber is unaltered as is the case during brief acute experiments. The oxygen consumption in cardiac hypertrophy cannot be compared with that of non hypertrophied fibers in an attempt to apply the Law of the Heart because the fibers are altered in structure and presumably modified in physical fitness. Furthermore since the weight of each hypertrophied fiber is increased and the number of fibers is unchanged a normal oxygen consumption per 100 gm of hypertrophied left ventricle actually denotes an increased oxygen consumption per hypertrophied fiber. This would tend to accord with Starling's Law of the Heart.

Similarly the observed normal oxygen consumption per 100 gm of failing myocardium[8] appears contradictory in view of an anticipated increased oxygen consumption because of the enlarged diastolic volume. But here too the physical fitness of the failing myocardial fibers has been altered and the Law of the Heart cannot be applied if comparison is made with normal myocardial fibers. Furthermore as the heart in failure is an hypertrophied heart a normal oxygen consumption per 100 gm of failing left ventricle actually represents an increased oxygen consumption per failing myocardial fiber. With moderate exercise the size of the heart has been observed to diminish slightly. Accordingly less oxygen utilization might be anticipated according to the Law of the Heart but Lombardo et al[44] actually determined that there was an increase in oxygen consumption according to the technique of coronary sinus catheterization and the nitrous oxide method. Bing Falholt and associates[7] concluded that an increase in initial length of the heart muscle fiber augmented oxidative myocardial metabolism only in the absence of chronic heart failure and that heart failure was accompanied by a defective conversion of oxidative energy into useful work. There is evidence suggesting that during exercise as well as in certain pathologic states nervous humoral or other factors increase the mechanical efficiency or the contractility of the heart muscle without an increase in the length of the muscle fiber or in the oxygen consumption[6, 49] Heart failure is characterized by a reduction in mechanical efficiency the total energy liberation as measured by oxygen consumption being maintained while the mechanical work performed is diminished[48]

ADAPTABILITY OF THE HEART

Cardiac Reserve

Normal cardiac function is characterized by a variability of performance which is remarkably adapted to changing demands. Thus the work of the heart may be increased six fold during exercise and its maximal output during running has been calculated as eight to ten times that of the resting state. The increased needs of the tissues for blood due to various other physiologic functions or pathologic states are satisfied by a corresponding enhancement of the cardiac output. Thus in health and disease the heart is potentially capable of a wide range of increased work

performance beyond that required under basal conditions. The extent of this potentiality is known as the *cardiac reserve*. A reduction in cardiac reserve is the first step on the pathway to cardiac failure. The severity of cardiac disability is measured by the degree of impairment of the cardiac reserve.

The cardiac reserve is related in part to Starling's Law of the Heart. The greater energy of cardiac contraction accompanying an increased diastolic volume is analogous to the more forceful contraction of a strip of skeletal muscle the greater the initial load, i.e., its initial length.[3] Although the force of cardiac contraction has been related to the initial tension by some observers,[19, 61, 15] the weight of evidence supports Starling's conclusion that it is dependent on the initial length of the myocardial fibers.[3] According to the latter concept, increased length of the fibers is associated with a more forceful contraction because of the greater surface area available for chemical activity. This increased energy response with increased initial fiber length may be a fundamental property of the contracting muscle protein, actomyosin.[65] The reserve of the heart is due to the reserve of the individual fibers and the latter in turn depends on their potential ability to undergo an increase in length. Up to a physiologic limit this is accompanied by greater chemical and mechanical energy. Beyond this increased length is accompanied by a diminution in the force of contraction.

Clinically, the cardiac reserve may be theorized as being the difference between the length of the cardiac fibers at rest and their length when the physiologic limit of stretch is reached. If as a result of cardiac disease the cardiac fibers are so elongated that they approach their physiologic limit when the individual is at rest, the cardiac reserve is diminished to virtually zero and the heart may be unable to adapt itself adequately to the increased demands of physical exertion or other physiologic or pathologic strains.

Cardiac Tonus or Tone

There is considerable confusion in the definition and usage of the term "tone" or "tonus," as applied to the heart. Meek[50] has reviewed the evidence which indicates that cardiac tonus in the physiologic sense of a "sustained partial contraction" in diastole does not exist. Tonus has been defined as the degree of resistance to deformation, which according to Kabat and Visscher[34] represents the elasticity of the heart muscle. A diminution in elasticity is correlated with decrease in the external work of the heart and eventually with cardiac failure.

Clinicians often employ the term "cardiac tone" in an ill defined manner to indicate the quality of cardiac contraction. In this sense it is erroneously supposed that the more enlarged the heart, the poorer the tone. The tone of the heart muscle is also supposed to be indicated by the quality of the cardiac sounds. A useful concept of cardiac tone is that proposed by Starling,[69] i.e., the physiologic fitness or mechanical efficiency of the muscle fiber. Thus in the heart lung preparation, when the heart deteriorates after several hours its fibers must have a greater initial length to do the same work that it did when it was fresh. The tone or mechanical efficiency of the muscle fiber is said to be diminished. A heart with good muscular tone may undergo only a slight increase in diastolic volume in order to overcome an elevated arterial resistance, while a diseased heart with poorer tone ("physiologic fitness") may have to dilate much more to accomplish the same work. Starling's Law of the Heart[59] may still apply to the fatigued heart in that a greater diastolic volume results in a greater energy of contraction. But the poorer the cardiac tone the smaller the increment in mechanical work effected by each unit increase in length of the cardiac fibers. Failure of the heart is thus characterized by a decreased capacity for doing work at a given fiber length or at a given diastolic volume.

Reflex Control of Cardiac Output

According to Starling's Law of the Heart the strength of ventricular contraction and the size of cardiac output are determined rather passively by changes in diastolic volume and the consequent degree of stretch of the myocardial fibers. Stead and Warren[62] documented evidence to the effect that the ventricles are actively concerned in determining cardiac output. The cardiac output was found to be independent of wide variations in atrial pressure. A reduction in arterial pressure induced an immediate rise in cardiac output which appeared too rapidly for a humoral mechanism. They suggested that afferent stimuli arising from a reduction in arterial pressure, movement of the limbs during exercise or emotional thoughts produced a

reflex stimulation of cardiac output according to variations in activity and needs. But the possibility is not excluded that such reflexes vary cardiac output not by direct modification of ventricular contraction but by first altering the venous inflow. Factors which reduce the peripheral resistance and thereby increase the speed of circulation ultimately augment cardiac output by enhancing the venous return to the heart. Increase in heart rate without elevation of the stroke output may increase the cardiac output per minute without enlarging the diastolic volume. Factors which improve the physical fitness or mechanical efficiency of the myocardial fibers can evoke an increased stroke and minute output without increasing diastolic volume. There is evidence also that in the *intact animal* the blood pressures in the aorta and in the pulmonary arteries, the autonomic nerves, and hormones such as epinephrine and norepinephrine affect the contractility of the heart and regulate cardiac performance in the same sense as the initial length of the cardiac fibers (end-diastolic volume).[37]

Factors Impairing Cardiac Output

An inadequate cardiac output may result from (1) a deficient venous return, (2) impaired cardiac contraction, (3) increased resistance to cardiac outflow.

1. Except momentarily, the output of the heart is equal to the venous return to the heart. Any reduction in venous return is rapidly mirrored in a corresponding reduction in cardiac output. The venous return may be gauged essentially by the amount of the circulating blood volume and by the speed with which this returns to the heart. Reductions in venous return usually follow a loss of circulating blood volume due to hemorrhage, loss of plasma or severe dehydration, or the venous return may be curtailed by mechanical obstructions to cardiac inflow. Occasionally the venous return falls to a completely inadequate amount following prolonged standing or in some individuals following a change from the recumbent to the erect position. This is due to a pooling of blood in the lower portions of the body because of a failure of sympathetic vasoconstrictor or other mechanisms to maintain an adequate venous return to the heart against the force of gravity. Not only the output of the heart as a whole but the output of each of its chambers is conditioned by the quantity of blood which is brought to it. Therefore the inflow of blood and the output from the right or left ventricle tend to be diminished if there is an obstruction or stenosis of the tricuspid or mitral valves respectively.

2. Impaired cardiac contraction or a diminution in its physiologic fitness accounts for the great majority of instances of inadequate cardiac output and therefore of cardiac insufficiency. This is usually the result of a deficient blood supply (coronary insufficiency) or of diseases which damage the heart muscle or impair its physiologic efficiency. As we shall see, the *normal* cardiac muscle can long compensate for many serious loads imposed by cardiovascular or other diseases and still accommodate to the strains of vigorous activities. But with a reduction in myocardial strength and efficiency, overloading of the heart and inadequacy of output occur with progressively smaller stresses.

3. Increased resistance to outflow tends to reduce the cardiac output from the atria into the ventricles if there is an atrioventricular valvular stenosis, or from the ventricles into the great vessels if there is an aortic or pulmonic valvular stenosis. Hypertension with its increased peripheral resistance tends to reduce the output of the left ventricle.

Other factors which tend to reduce the cardiac output and thereby provoke heart failure include the valvular insufficiencies which cause a regurgitation of some of the expelled blood. Thereby the effective blood flow to the tissues is less than the original ventricular output by the amount regurgitated. Similarly in shunts between large arteries and veins or between the right and left sides of the heart, the actual blood flow to the tissues is diminished by the quantity of shunted blood.

Finally the output may be inadequate in relation to inordinate requirements of the tissues because of excessive metabolism, e.g., hyperthyroidism, or because the normal quantity of blood is deficient in hemoglobin (anemias), vitamins (beriberi), or oxygen (advanced pulmonary emphysema). In the latter circumstances adequate amounts of oxygen, vitamins, etc., can be provided only by augmented cardiac outputs. In many cases inadequacy of cardiac output is the result of a combination of factors, e.g., an increased demand of the tissues plus myocardial impairment in cases of anemia, or increased resistance to outflow plus myocardial

damage in cases of hypertension with advanced coronary atherosclerosis

The following sections are concerned with the compensatory mechanisms by which the heart and circulation long maintain an adequate output despite these factors

CARDIAC AND CIRCULATORY COMPENSATIONS

Compensation and Decompensation

A number of cardiac and circulatory compensations serve to restore an adequate output whenever the latter is threatened by disease *When these adjustments succeed in maintaining an adequate blood flow without distressing symptoms the heart and circulation are said to be in a state of compensation*

Compensation may be complete or incomplete Compensation is complete when the strain of the disease has been overcome, yet sufficient cardiac reserve remains to meet adequately the diverse demands of an active physical life Incomplete compensation or cardiac decompensation denotes a substantial expenditure of the cardiac reserve in order to overcome the load imposed by disease, the remainder is such that unpleasant symptoms develop with slight or moderate activity When the heart is adjusted to the disease factor but has no reserve for physical exertion the heart is said to be compensated only at rest

Types of Cardiac and Circulatory Adjustments

1 The primary compensations concern the heart directly and include tachycardia cardiac dilatation and cardiac hypertrophy

2 When these primary compensations fail to restore or maintain an adequate cardiac output renal retention of sodium and water tends to increase the blood volume and thereby the venous return (Chapter 8) Within certain limits this tends to restore an adequate cardiac output

3 *If the reduction in cardiac output is severe* and occurs very rapidly (within a few hours) a significant augmentation of blood volume and venous return cannot be effected Instead the deficient output is reapportioned so as to divert its major fraction to the vital brain and heart (Chapter 12)

4 A deficiency in cardiac output may be compensated also by metabolic hematologic and other adjustments e g an increase in erythrocytes in cases of congenital heart disease or chronic pulmonary disease, or increased extraction or utilization of the oxygen available in the transported blood Other cardiac factors of safety have been enumerated by Alexander and Wiggers [2]

CARDIAC COMPENSATION BY TACHYCARDIA

The cardiac output (minute volume of blood flow) is equal to the product of the stroke output and the cardiac rate *When the* cardiac output must be augmented to accommodate increased tissue demands due to exercise this is accomplished by both an increase in rate and an increase in output Of the two, the acceleration in rate is the less efficient mechanism In the heart lung preparation studied by Starling and Visscher it was found that a given unit of work was performed more efficiently i e with a lesser consumption of oxygen the slower the cardiac rate [60] In athletes and subjects who have undergone a period of training a physiologic enhancement of minute volume is accomplished essentially by an increased output per beat and to a lesser extent by an increased cardiac rate [12]

Similarly when the cardiac output is inadequate because of disease, it can be increased and restored to normal levels either by tachycardia or by augmented stroke output As a rule tachycardia appears only as a transient compensatory mechanism especially with sudden increases in cardiac demands More efficient and more permanent compensation results from cardiac dilatation and hypertrophy which augment the total output by increasing the output per beat

An accelerated heart rate (tachycardia) appears not only as a compensation for an inadequate cardiac output but also as a result of a variety of unrelated conditions When a deficient output is compensated by dilatation and hypertrophy the heart rate is usually normal However muscular exercise in the subject with cardiac dilatation and hypertrophy often induces a greater acceleration of the heart rate and greater persistence of such tachycardia at the conclusion of activity than is found in the normal person When the cardiac output is uncompensated despite cardiac dilatation hypertrophy and other mechanisms (i e in heart failure) tachycardia is often present despite minimal activity Tachycardia is the major cardiac compensation when the stroke output cannot be increased either because of severe acute

myocardial injury or because of a sharply reduced blood volume and venous inflow into the heart (shock)

The compensatory value of tachycardia is limited by the shortening of diastole and consequent reduction in ventricular filling as the rate increases Experiments with the heart lung preparation have shown that beyond the rate of 180 beats per minute the reduction in ventricular filling and ventricular output becomes so great that further increases in cardiac rate actually reduce the total minute volume [8]

Pathogenesis of Compensatory Tachycardia

A compensatory increase in heart rate is effected by various mechanical chemical and nervous stimuli which diminish the tone of the cardioinhibitory center and vagus nerve and increase that of the cardioaccelerator centers and accelerator fibers in the sympathetic nerves [illegible] A fall in aortic and carotid arterial pressure as the cardiac output is reduced inhibits the carotid sinus and aortic depressor nerves and reflexly reduces vagal tone [27, 31, illegible] At the same time an inadequate output tends to be associated with stasis and elevation of pressure in the vena cava and right atrium This may stimulate receptors which reflexly cause cardiac acceleration by inhibiting the vagus and stimulating the accelerator center and fibers (Bainbridge reflex) [5] (The site and significance of this reflex have been amplified by Nonidez[31] and questioned by DeGraff and Sands[13] and by Anrep and Segall [4]) The secretion of epinephrine and the accumulation of metabolites as the output falls may also be concerned in effecting a compensatory tachycardia The exact mechanisms are uncertain

CARDIAC DILATATION

Cardiac dilatation denotes an increased capacity of the cardiac chambers Its compensatory action is explained by the Law of the Heart (p 85) Since the length of the muscle fiber determines the mechanical energy set free ' or the strength of contraction dilatation of the heart by elongating myocardial fibers results in more work and an increased stroke output The greater effectiveness is probably due to the larger surface area of elongated fibers available for active physicochemical processes The extent of cardiac dilatation necessary to compensate a given load due to cardiovascular disease increases as the load increases or as the physiologic fitness of the myocardium diminishes On the one hand the dilated myocardium possesses the advantage of greater work performance according to Starling's Law as well as a lesser degree of shortening per muscle fiber to eject a given volume of blood during systole than is required in the normal heart [11] On the other hand the dilated heart must support a greater load and expend a greater amount of energy to attain the same cardiac output

Cardiac enlargement chiefly due to dilatation of its chambers is the commonest manifestation of any cardiovascular disease which tends to impair the cardiac output Furthermore the dilatation is localized or most conspicuous in that cardiac chamber or even in that portion of a chamber, which is subjected to the greatest strain The frequent observation that individuals with cardiac enlargement are long able to maintain good circulatory function, supports the concept that cardiac dilatation is a mechanism for compensating cardiovascular lesions which tend to interfere with an adequate cardiac output

Cardiovascular Diseases and Compensatory Dilatation

Cardiac dilatation may result from (1) mechanical lesions (2) myocardial lesions or often a combination of both

1 *Mechanical lesions* tend to increase the diastolic volume and thereby cause cardiac dilatation by (a) increasing the venous return to the heart e g in cases of arteriovenous aneurysm (b) increasing the resistance to outflow from one of its chambers e g mitral or aortic valvular stenosis or hypertension (c) permitting a reflux of blood into a chamber after it is ejected, e g in aortic valvular insufficiency

2 *Myocardial lesions* tend to impair cardiac contraction and diminish cardiac output while the inflow is temporarily unchanged This causes an increase in the diastolic volume and cardiac dilatation (e g myocardial infarcts secondary to coronary occlusions rheumatic myocarditis etc) However the experimental destruction by cautery of 75 to 95 per cent of the free wall of the right ventricle of the dog is not followed by any significant rise in venous pressure or alteration in pulmonary artery pressures [61, illegible] The mechanism of compensation and maintenance of right ventricular output is uncertain [illegible]

Most frequently cardiac contraction is im

paired by coronary artery disease or rheumatic myocarditis at the same time that a mechanical strain is imposed by hypertension or valvular defects. Whether due to a mechanical lesion or to an impaired myocardial contraction, dilatation results from an inability of the affected chamber to expel an increased venous return or to eject a normal venous return against an abnormal obstruction or a regurgitant stream.

The normal ventricle does not empty itself completely during systole but leaves a *residual volume* which, in the case of the right ventricle, varies from 25 to 160 cc but averages about 50 cc per square meter of body surface area.[30, 9, 45] The end diastolic volume, or volume of blood in the ventricular cavity during isometric contraction, determines the stretch on the myocardial fibers and therefore influences the strength of contraction. It is equal to the sum of the stroke output plus the residual volume. In heart failure the diastolic volume, the residual volume and the ratio of the residual to the stroke volume are increased.

When heart failure occurs, the compensatory mechanisms may be said to have failed in restoring an adequate cardiac output. However, they continue to operate. If a moderate degree of cardiac dilatation effects the needed increase in cardiac output, this remains unchanged so long as the status of the myocardium and the mechanical lesion remain unchanged. If the cardiac output is definitely inadequate despite a given degree of dilatation (i.e., cardiac failure ensues), the heart continues to dilate in a futile compensatory effort. The enlarged circulating blood volume which is an essential feature of chronic heart failure contributes significantly to the increased diastolic volume and cardiac dilatation. Thus the most rapid and pronounced degrees of cardiac enlargement are observed in the failing heart.

CARDIAC HYPERTROPHY

Cardiac hypertrophy denotes an increase in the weight of the heart associated with an enlargement of the individual muscle fibers. Pseudohypertrophy and false hypertrophy are terms that have been applied to hearts whose weights are increased not by enlargement of muscle fibers but by edema as in beriberi, or by glycogen infiltration. It had been generally accepted that cardiac hypertrophy is associated with an increase in the diameter and volume of the individual fibers but with no increase in their number.[26] But studies by Linzbach suggest that this may apply only to hearts which are hypertrophied to a total weight of 500 gm. Beyond that point the thickened hypertrophied fibers may split longitudinally and produce an increase in the number of fibers.[44]

Cardiac hypertrophy may sometimes be surmised from clinical and roentgenologic studies, especially angiocardiography, but essentially it is a postmortem diagnosis based on the weight of the heart, the thickness of chamber walls or gross and histologic examination. Hypertrophy of individual chambers may be similarly determined by dissection and by weighing.[8, 41, 1] Normally the heart weighs 0.43 per cent of the body weight in men, 0.40 per cent in women.[illegible] The heart weight is directly proportional to muscular development and therefore in obese individuals the percentage of heart to body weight is less than in muscular persons. A heart weighing *more than 400 gm. in an adult male* or more than 375 gm. in an adult female [illegible] practically always hypertrophied. [illegible] rule weights exceeding 350 gm. and 300 gm. respectively denote cardiac hypertrophy. At birth the percentage of heart weight to body weight averages 0.62 per cent for males and 0.55 per cent for females. In old age there is usually *some atrophy of the heart*.

According to Fulton and coworkers[21] the normal total ventricular weight is less than 250 gm., the free wall of the right ventricle weighs less than 65 gm. and the combined weight of the left ventricle and ventricular septum is less than 190 gm. The left ventricle is regarded as hypertrophied if, together with the septum, it weighs 225 gm. or more. Right ventricular hypertrophy is indicated if the free wall of the right ventricle weighs 80 gm. or more or if the ratio of its weight to that of the combined weight of the left ventricle and septum is greater than 1:2. In hearts with isolated right ventricular hypertrophy, the total ventricular weight may fall within normal limits. The normal thickness of the left ventricle midway between apex and mitral valve is 10 to 12 mm., that of the right ventricle midway between apex and pulmonary valve is 3 to 4 mm.

The determination of dilatation and hypertrophy of individual segments of the various

chambers at necropsy examination has been described by Kirch.[89]

The Compensatory Nature of Cardiac Hypertrophy

That cardiac hypertrophy is a compensatory mechanism is concluded from the experimental pathologic and clinical observations that (1) it appears when there is a disturbance which tends to interfere with normal cardiac function, (2) it is localized in the chamber or chambers affected by the disturbance, (3) after its development normal cardiac function is frequently restored.

Experimental evidence indicates that the hypertrophied heart not only maintains the normal circulation despite a cardiovascular lesion but also retains an adequate reserve for unusual circulatory demand. Hasenfeld and Romberg[4] produced aortic insufficiency in rabbits hearts and observed the development of cardiac hypertrophy. They concluded that the reserve strength of the heart was not impaired and that cardiac hypertrophy is a sign of increased strength. Similarly Wolfer[3] observed that rabbits hearts which had become hypertrophied after experimentally produced aortic stenosis or repeated injection of epinephrine responded perfectly to increased physical demands. Dieckhoff[14] actually found that in acute experiments the experimentally hypertrophied heart displayed an increased capacity for work when compared to the normal heart.

From clinical and pathologic studies it is clear that cardiac hypertrophy is not incompatible either with normal activity or with long life. I have observed individuals who in spite of their enormous hearts associated with aortic stenosis or insufficiency have engaged in the severest athletics and lived a normal span of life. For practical purposes no distinction could be made between the physical capabilities of these individuals and those of persons with normal hearts.

There are many unanswered questions regarding the nature dynamic properties and pathogenesis of cardiac hypertrophy. The concept that the hypertrophied myocardial fiber is stronger than the normal fiber or that it imparts greater strength of contraction to cardiac muscle has been questioned.[4]

Relation of Cardiac Dilatation and Cardiac Hypertrophy

Cardiac hypertrophy and cardiac dilatation are both compensatory mechanisms. Cardiac dilatation appears to be the immediate response of the heart when it must expel a constant or increased volume of blood against an increased resistance or an increased volume against a constant resistance. While the dilated heart overcomes these obstacles it does so with less mechanical efficiency than the normal heart and by encroaching on the cardiac reserve. It may be that cardiac hypertrophy is a more efficient long term compensatory response to similar cardiovascular disturbances but it requires more time to develop.[34]

Experimental and pathologic evidence indicates that cardiac dilatation and hypertrophy are responses to the same stimuli dilatation occurring immediately and hypertrophy after some time and probably as a result of unknown physicochemical changes induced by the primary dilatation. The lengthening of muscle fibers associated with cardiac dilatation allows a greater surface area for the diffusion of metabolites which may aid in the growth of the fibers. Horvath[33] first emphasized that the development of cardiac hypertrophy was dependent on and preceded by cardiac dilatation. Eyster Meek and Hodges[17] showed that following experimental aortic insufficiency and aortic stenosis in dogs dilatation occurred rapidly and reached a maximum in three to six days. Hypertrophy developed subsequently and was maximal only after one hundred days.

In human pathology cardiac dilatation and hypertrophy are almost always associated and localized in the same portions of the heart. This indicates that they are responses to the same stimulus. Sometimes it can be demonstrated that dilatation precedes hypertrophy. Thus in cases of acute glomerulonephritis death from cardiac failure occasionally occurs in the first week of the illness. The hearts show definite dilatation but no hypertrophy. On the other hand if death occurs after a month a significant degree of hypertrophy is present.

Pathogenesis of Cardiac Hypertrophy

Many theories have been proposed to explain the development of cardiac hypertrophy.[65, 29]

1 *The theory of work hypertrophy* imputes cardiac hypertrophy to an increase in the work of the heart. Observations in animals indicate that the size of an animal s heart increases in proportion to the amount of activity necessi

tated by its mode of life and that cardiac hypertrophy can be induced by exercising dogs[42] Clinical and pathologic observations disclose that hypertrophy of a chamber occurs when its work is increased in compensation for a valvular or circulatory abnormality

2 *The nutritional theory* attributes cardiac hypertrophy to a defective blood supply and is based largely on the development of hypertrophy in clinical and experimental anemia and the belief that cardiac hypertrophy in arteriovenous aneurysm and aortic insufficiency is due to a deficient coronary circulation[4]

3 *The injury theory* suggests that cardiac hypertrophy is a reaction to tissue injury which acts as a pathologic nutritive stimulus[1, 17]

4 *The muscular stretch theory* suggests that the fundamental cause of hypertrophy is the stretching of muscle fibers[23] This is not necessarily contradictory to the above theories but more clearly and precisely defines their application Stretching of myocardial fibers results whenever the diastolic volume and pressure are increased by enhanced inflow impaired myocardial contraction or increased resistance to outflow This is the stage of cardiac dilatation

The lengthening of muscle fibers results in a greater surface area for an unchanged mass of muscle This permits a relatively greater nutritive diffusion surface between blood and fiber and therefore leads to the fiber's growth In due time the dilated fibers become hypertrophied This explains the development of cardiac hypertrophy following dilatation in cases of valvular and vascular lesions as well as in instances of myocardial disease Hormonal factors especially the growth hormone may be concerned in the development of cardiac hypertrophy [8] Progressive heart failure is a potent factor in pronounced cardiac hypertrophy because it is responsible for a progressive increase in diastolic volume and consequent muscle stretch On the other hand, increased work of the heart does not cause hypertrophy if the additional work is due exclusively to tachycardia while the stroke output is not enhanced, as in most cases of uncomplicated hyperthyroidism Finally, there are many unknown extrinsic or intrinsic factors controlling the metabolism of the muscle fiber which may account for the marked difference in the degree of hypertrophy experienced by different hearts in response to apparently similar pathologic disturbances Hearts in aortic stenosis have varied from virtually normal weight to over 2000 gm,[48] sometimes without quantitative correlation to the degree of stenosis or duration of illness Although marked hypertrophy is the rule in cases of hypertension with heart failure little or no hypertrophy has been found at autopsy in the hearts of some patients with these conditions[49]

Reversibility of Cardiac Dilatation and Hypertrophy

Roentgenologic observations have disclosed that cardiac enlargement (dilatation and hypertrophy) is reversible even when it has been present for years provided that the causative disturbance is abolished or alleviated[46] Cardiac enlargement has been seen to diminish with regression of the symptoms of heart failure and to disappear completely or diminish with (a) subsidence of acute glomerulonephritis (b) correction of anemia, (c) surgical correction of an arteriovenous aneurysm patent ductus arteriosus coarctation of aorta or hyperthyroidism with heart failure (d) adequate thyroid administration in myxedema heart disease (e) vitamin B and protein therapy in beriberi heart disease (f) sympathectomy in hypertensive heart disease

That cardiac hypertrophy as well as dilatation is reversible is indicated by the case of arteriovenous aneurysm due to congenital cavernous hemangioma reported by Matas and Heninger[47] The greatly enlarged heart in this case was restored to normal size as determined roentgenologically following surgical removal of the hemangioma Because cardiac enlargement had been present at least four years Matas and Heninger believed there must have been hypertrophy as well as dilatation and that hypertrophy like dilatation could regress when the cause was removed Electrocardiographic and roentgen ray studies of the heart in hypertensive heart disease before and after sympathectomy also indicate that ventricular hypertrophy is reversible (p 949)

CIRCULATORY COMPENSATION BY INCREASED BLOOD VOLUME AND VENOUS RETURN

When cardiac dilatation and hypertrophy with or without tachycardia are no longer capable of maintaining an adequate cardiac

output the cardiac reserve is largely expended and there is an insufficient blood supply to the tissues. This deficiency in blood flow may occur only with physical exertion or in extreme cases even with the patient at rest. At this stage extracardiac compensatory mechanisms are invoked and these may partially or completely restore the cardiac output for a variable period.

Briefly a diminished cardiac output causes a deficient blood flow to the kidneys and other organs and tissues which in some manner results in a retention of sodium and water and a corresponding increase in the circulating blood volume. The latter augments the venous return and thereby stimulates the failing ventricle to restore an adequate output according to the Law of the Heart. This compensatory mechanism will be discussed in detail in the chapter on the pathogenesis of congestive heart failure (Chapter 8).

CIRCULATORY COMPENSATION BY REDISTRIBUTION OF A DIMINISHED CARDIAC OUTPUT

A significant compensatory increase in blood volume can be effected only over a period of days or weeks. Furthermore this compensatory mechanism is most effective when the reduction in cardiac output is relatively small (10 to 30 per cent). When a diminution in cardiac output occurs rapidly (in a few hours) and is of pronounced degree (35 per cent or more) a restoration of cardiac output cannot be rapidly accomplished by an increased blood volume or by any other means. A slight immediate compensatory increase in circulating blood volume may occur as a result of an intravascular influx of extracellular or intracellular fluid but this is clinically insignificant.

To preserve the life of vital organs such as the brain and heart the little blood flow available is redistributed in such a way as to divert most of it from the periphery and splanchnic areas to more vital structures. This is probably accomplished in large measure by reflex inhibition of carotid sinus and aortic depressor tone, by promoting the secretion of norepinephrine and perhaps by direct anoxemic stimulation of the vasomotor center—all of which produce sympathetic vasoconstriction especially of the skin and splanchnic viscera. This compensatory mechanism is discussed more fully in the section on the pathogenesis of acute circulatory failure or shock (Chapter 12). Vasoconstrictive redistribution of blood also occurs in the more chronic and milder forms of deficient cardiac output, but it is less important than the mechanism of increased blood volume.

Relation of Compensatory Mechanisms to Clinical Manifestations of Cardiac and Circulatory Dysfunction

Except in occasional instances of extreme and acute reduction of cardiac output, symptoms of circulatory deficiency are not due directly to the inadequate output. In cases of irreversible and fatal shock, syncope and sudden death the compensatory mechanisms have failed to maintain an adequate output to supply vital organs notably the brain; temporary unconsciousness or death is actually due to the deficient output. As a rule however despite serious cardiovascular disease the blood flow to the brain and heart is adequately maintained by the enumerated compensations. Under these circumstances the clinical manifestations of the cardiovascular diseases which have threatened the adequacy of the circulation are determined not by insufficient output but by the compensations which restore that output.

In the mildest cases a falling cardiac output is adjusted by cardiac dilatation and hypertrophy which are denoted clinically by signs of enlargement of the heart. The patient is said to have compensated heart disease. The compensations (cardiac dilatation and hypertrophy) are the evidence of cardiovascular disease. Although beneficent in their effect on cardiac output they are abnormal in that they denote the existence of a serious disease which requires cardiac compensation and in that they expend some of the reserve power of the heart. Furthermore the enlarged hypertrophied heart has increased muscle mass without a corresponding increase in the number or size of the blood vessels. This disparity predisposes to myocardial inefficiency and heart failure (p. 128). Thus cardiac enlargement may be considered as a compensatory process (Chapter 4), as an evidence of cardiovascular disease (Chapter 5) and as a mechanism predisposing to heart failure (Chapter 6).

When extracardiac compensations must be invoked to maintain an adequate cardiac output, clinical evidence of cardiac or circulatory failure appears. Here also the clinical manifestations are not entirely the direct result of a deficient cardiac output but also of the

compensatory mechanisms which attempt to restore that output Since heart failure or circulatory failure is defined in terms of clinical phenomena and these are produced by circulatory compensations as well as by deficient output heart failure may be present despite an adequate output The deficient output initiates the compensatory mechanism but the compensatory mechanism produces symptoms

When the extracardiac compensation is chiefly that of increased circulating blood volume, the resulting clinical phenomena are those of chronic circulatory or cardiac failure When the extracardiac compensation is chiefly that of redistribution of a greatly diminished output the compensatory process leads to the clinical phenomena known as acute circulatory failure (shock) Syncope and death are often manifestations of acute circulatory failure and are actually due to the deficient output itself in such instances the compensation of redistribution of blood to the vital brain has failed temporarily or permanently

Accordingly the following classification of circulatory failure is proposed

CLASSIFICATION OF CIRCULATORY FAILURE

I—Chronic circulatory failure (congestive heart failure)
- A—Left-sided heart failure
- B—Right-sided heart failure
- C—Combined left and right sided failure
- D—Heart failure due to prolonged or chronic *interference with inflow*
  1. Constrictive pericarditis
  2. Persistent severe tachycardias
- E—Heart failure associated with increased *venous return (high output failure)*
  1. Arteriovenous aneurysm
  2. Chronic severe anemias
  3. Beriberi
  4. Hyperthyroidism
  5. Pulmonary emphysema
  6. Paget s disease

II—Acute circulatory failure (Chapter 12)
- A—Shock
- B—Syncope
- C—Sudden death

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Chapter 5

ENLARGEMENT OF THE HEART

This chapter is concerned with cardiac dilatation and hypertrophy not as compensatory mechanisms but as evidences of myocardial valvular or circulatory disease In clinical discussions the term cardiac enlargement is employed to signify dilatation and/or hypertrophy, because the determination of the presence and degree of each of the latter is extremely difficult

Clinical recognition of cardiac enlargement depends chiefly on physical and roentgenologic examination The presence of cardiac enlargement may also be indicated or confirmed by the electrocardiographic findings Cardiac enlargement not only denotes the presence of cardiac disease but also, because of its characteristic localizations may suggest the exact nature of the cardiac lesion

PHYSICAL SIGNS OF CARDIAC ENLARGEMENT

The chief physical signs of cardiac enlargement are displacement of the apex beat as determined by inspection and palpation or displacement of the cardiac borders as determined by percussion As a rule cardiac enlargement is present when the maximum apical impulse is situated lateral to the midclavicular line or more than 10 cm from the midsternal line in the fifth left intercostal space or below the level of the fifth intercostal space Cardiac displacement due to bronchopulmonary lesions may similarly affect the position of the apical impulse In many persons it is difficult or impossible either to see or clearly to feel the apex beat

Cardiac enlargement may also be denoted by an accentuated or diffuse apical impulse The accentuated apical impulse due to hypertrophy of the left ventricle was considered characteristic of aortic insufficiency by Bard [2] who termed the pulsation "choc en dome Enlargement of the right ventricle may be suggested by a pronounced epigastric pulsation A precordial bulge is often observed in children with cardiac enlargement due to rheumatic or congenital cardiac disease Distinctive pulsations of the chest wall have been associated with individual cardiac lesions [15]

Percussion discloses cardiac enlargement or displacement if cardiac dullness extends beyond 10 cm to the left of the midsternal line in the fifth interspace It may denote either left or right ventricular enlargement If cardiac dullness extends more than 4 cm from the midsternal line in the third left interspace, there is probably enlargement of the left atrium dilatation of the pulmonary artery or possibly enlargement of the pulmonary conus of the right ventricle The value of percussion of the right side and base of the heart is more limited except in cases of gross enlargement The accuracy with which cardiac enlargement can be discovered by percussion is impaired in very obese individuals in those with a very muscular chest wall in subjects with pronounced pulmonary emphysema and in women with large breasts Despite the imperfections of these physical methods the physician should refine his skill in them because they are the only means of discovering cardiac enlargement at the bedside when the patient is too ill or facilities are not available for roentgen ray examination

ROENTGENOLOGIC DIAGNOSIS OF CARDIAC ENLARGEMENT

Often single examinations are inconclusive as to the presence of cardiac enlargement But when permanent records are made at intervals, a comparison of these records may reveal significant changes in size indicative of cardiac enlargement

The size of the heart and the presence of generalized or local cardiac enlargement may be determined by fluoroscopy orthodiagraphy

and teleoroentgenography In special instances especially in cases of congenital heart disease and to distinguish cardiac enlargement from an extracardiac mass angiocardiography has proved to be valuable When performed with *simultaneous exposures in* two projections at right angles to each other (p 15) it permits a three-dimensional appreciation of the size and configuration of the cardiac chambers and more accurate assessment of cardiac enlargement Kymography and electrokymography may aid in distinguishing cardiac enlargement from pericardial enlargement and ventricular aneurysm Tomography (planigraphy) has been recommended to distinguish left from right ventricular enlargement a distinction which is both difficult and important in differentiating mitral stenosis from mitral insufficiency

In clinical practice cardiac enlargement is most commonly discovered or verified by fluoroscopy Although this method is largely subjective it is surprisingly accurate when used by one who attains skill with persistent study and experience *Fluoroscopy* is especially useful in recognizing enlargement of individual cardiac chambers, this is aided by rotating the patient so as to obtain multiple views of the cardiac silhouette and by observing the indentation of the heart on the barium filled esophagus

CARDIAC MENSURATION

For more objective determination of cardiac enlargement orthodiagraphs or roentgenographs of the chest at 2 meters distance are used *to measure various dimensions of the* posteroanterior cardiac silhouette[11] (Fig 37) These measurements are then compared with predicted measurements for height weight or surface area and sex as noted in available tables (Fig 38) The determination of cardiac enlargement may be based on calculation of the area of the frontal cardiac silhouette or of the volume of the heart (p 101) but these methods while theoretically more accurate are relatively difficult and rarely used

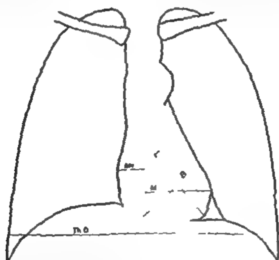


Fig 37 Cardiac diameters of normal heart in Fig 1 Mr = 4 1 cm Ml = 7 3 cm TD (transverse diameter) = Mr + Ml = 11 4 cm Internal thoracic diameter Th D = 30 5 cm L (long diameter) = 13 4 cm B (broad diameter) sum of perpendiculars to L = 10 4 cm

Cardiothoracic Ratio

The cardiothoracic ratio has often been used as an index of cardiac enlargement [12] This is the ratio of the transverse diameter of the heart (p 100) to the internal diameter of the chest at its widest point just above the level of the dome of the diaphragm If the cardiothoracic ratio significantly exceeds 50 per cent it is assumed that there is cardiac enlargement This is *only* a rough guide and is often inaccurate as the relationship between the diameter of the heart and that of the chest varies considerably [10]

The Transverse Diameter

The transverse diameter (p 100) which bears a definite relation to body surface area

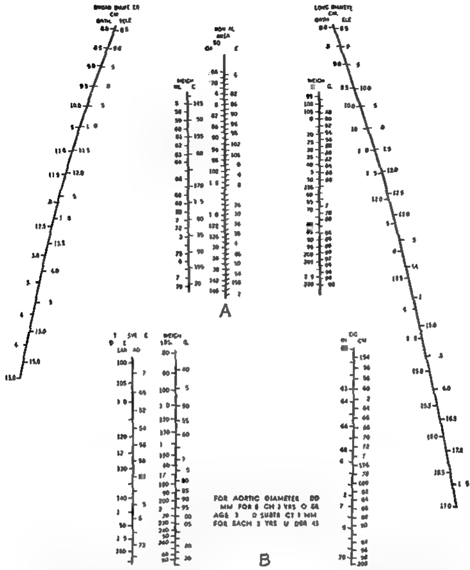


Fig 38 *A* Nomogram for prediction of frontal area of cardiac silhouette and for actual area from long and broad diameters (Ungerleider—Gubner) Extension of line connecting height and weight gives predicted area and connecting long and broad diameters gives actual area

B Prediction table for transverse diameter of cardiac silhouette (Ungerleider—Gubner) The theoretical transverse diameter of the heart (left column) is obtained by extension of line connecting height and weight Actual transverse diameter exceeding predicted value by more than 10 per cent is abnormal

or to height and weight has proved more valuable as an objective criterion of cardiac enlargement The transverse diameter (T or H) is the sum of the perpendicular from the outermost point of the right cardiac border to the midsternal line (MR) and the perpendicular from the outermost point of the left cardiac border to the midsternal line (ML) (Fig 37) In the erect position of the body, the transverse diameter averages between 10 and 13 cm, but even greater variations may occur normally Comparison of the measured transverse diameter of the heart with the prediction table of normal transverse diameter for given heights and weights[82] (Fig 38) gives a relatively accurate indication of cardiac enlargement [70] Similar tables for children have been prepared by Gordon and Adams [26] The tables for adults allow too high values for obese patients and are unsuitable in the presence of chest deformities, ascites or pregnancy When the measured transverse diameter exceeds the predicted value by more than 10 per cent the heart is probably enlarged when it exceeds the predicted value by more than 15 per cent the heart is almost always enlarged [81]

Certain limitations of this method must be recognized Some of the factors modifying the normal cardiac silhouette have been discussed (p 7) A transversely placed heart may suggest left ventricular enlargement In funnel breast with depression of the lower part of the sternum there is a flattening of the heart with apparent transverse enlargement The method of measuring the transverse diameter fails to consider the depth of the heart Thus the heart may be significantly enlarged by volume but not according to the transverse diameter This applies particularly to advanced obstructive emphysema with anteriorly directed enlargement of the right ventricle

The Long and Broad Diameters

Other measurements are employed to determine enlargement of individual portions of the heart The *long diameter* (or oblique diameter) of the heart (L) is the distance from the cardiac apex on the left to the junction of the right atrium with the superior vena cava or ascending aorta on the right The usual range of this dimension in the adult male is between 12 and 15 cm Normally the long diameter is about 1 5 cm or 10 per cent greater than the transverse diameter It is increased chiefly by enlargement of the left ventricle

The *broad diameter of the heart* (B) is the sum of the perpendicular (BR) from the point of junction of the right atrium with the diaphragm to the long diameter and the perpendicular (BL) from the point of junction of the left ventricle with the pulmonary arc to the long diameter The length of the broad diameter ranges between 8 and 11 cm in the adult male The broad diameter ranges between 65 and 85 per cent (average, 75 per cent) of the long diameter If the broad diameter exceeds 85 per cent of the length of the long diameter there is usually definite enlargement of the right ventricle

The Area of the Frontal Cardiac Silhouette

This area in relation to standards based on weight and height has been recommended as a criterion of cardiac size Ungerleider and Gubner[83] used the formula Area $= \frac{3}{4}\pi \times$ long $\times$ broad diameters and found that the calculated values showed a mean deviation of less than 3 per cent from the actual area as measured by planimetry They prepared a nomogram for direct reading without calculation of the frontal area when the broad and long diameters are known as well as for the prediction of the normal area from weight and height (Fig 38) The heart is considered enlarged if its frontal surface area exceeds predicted values by more than 10 per cent

Volume of the Heart

This may be determined most accurately by the actual volumetric reconstruction of the heart as a plastic model whose volume is equal to the amount of water it displaces when immersed The construction of such models has been described by Lysholm[53] Schatzki[66] and by Palmieri[59] The volume of the heart has been determined also from measurements of the area of the cardiac silhouette in the posteroanterior view and from the depth in the lateral view[45, 6] (See also Tomography p 7) Formulae for its calculation, suggested by Rohrer[63] by Kahlstorf[39] and by Jonsell[38] are based on the fact that the form of the heart is between that of an ellipsoid and a paraboloid The volume equals length $\times$ width $\times$ depth $\times$ 0 63 the latter being a constant used because the heart has the configuration mentioned rather than that of a three-dimensional solid Calculated thus the average volume of the heart ranges between 650 and 700 cc for the male and between 500 and 550 cc for the female According to Larsson and Kjellberg[45] the average normal cardiac volume is 785 cc for men 560 cc for women and as much as 1015 cc for athletes In general these calculations of cardiac volume have not proved of practical value in clinical practice

The total cardiac volume is the sum of the muscle volume of the heart plus the volume of blood in the cardiac chambers By determining the total heart volume by calculations as indicated and the volume of blood in the cardiac chambers by dye methods (p 223) the volume of cardiac muscle may be obtained by subtraction[2] The amount of blood in the heart in diastole was found to average 500 cc in males 320 cc in females and 685 cc in athletes Normally the amount of blood in the heart in diastole and the total cardiac volume are proportional to the total blood volume According to Sjostrand[72] in physiologic enlargement of the heart such as may occur in athletes the cardiac volume retains its normal relation to the total circulating blood volume in pathologic enlargement of the heart its volume increases out of proportion to the total blood volume



ENLARGEMENT OF THE INDIVIDUAL CHAMBERS

Cardiac enlargement may involve the entire heart, as in various toxic, infectious and metabolic diseases severe anemias and certain forms of combined left and right sided heart failure But in some of the most frequent and most important forms of cardiac disease especially in their less advanced stages, cardiac enlargement is confined to a single chamber or to two chambers These localized forms of enlargement are characteristic of certain diseases and are therefore of great diagnostic value Kirch[42] showed that enlargement may be confined not only to a single chamber but even to a special portion of that chamber The ventricles may be divided anatomically and physiologically into inflow and outflow tracts the inflow tract being the posterior segment of the ventricle between the atrial ventricular ostium and the apex, and the outflow tract being the anterior segment between the apex and the semilunar valve It is important to note that enlargement of the ventricles begins in the outflow tract first near the arterial ostium and then toward the apex, so that elongation of the chamber occurs Only later, when the inflow tract becomes enlarged is widening of the chamber seen roentgenologically Thus dilatation of a chamber may produce either elongation or widening Since it is more difficult to recognize the former roentgenologically, the earliest stages of cardiac enlargement may be overlooked

Left Ventricle

Early enlargement of the left ventricle begins in the outflow tract, involving the anterior wall and septum near the aorta Since this region is not part of the cardiac border in the dorsoventral silhouette it is not easily noted roentgenoscopically Moderate left ventricular hypertrophy with minimal dilatation (so called concentric hypertrophy) as seen in essential hypertension, may be characterized by moderate rounding of the left lower contour without significant alteration in cardiac diameters (Fig 39) An early evidence of left ventricular enlargement is the elevation and elongation of the lower left cardiac contour with corresponding shortening of the left middle contour With further elongation of the outflow tract the left ventricular border is lower and more closely in contact with the diaphragmatic shadow Later when the inflow tract also becomes enlarged, the apex of the left ventricle becomes broad rounded and displaced to the left, so that the transverse diameter may also be increased (Fig 40A)

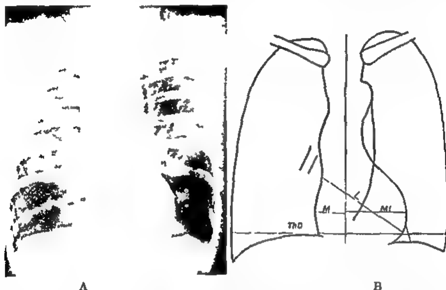


Fig 39 A Left ventricular hypertrophy in essential hypertension Increased convexity of left ventricular contour No increase in transverse or long diameters or in cardiothoracic ratio So-called concentric hypertrophy

B Sketch of *A* showing measurements Ml = 7 8 cm Mr = 3 8 cm TD = 11 6 cm ThD = 27 6 cm L = 12 6 cm

Although the transverse diameter may be increased with left ventricular enlargement there is usually a greater increase in the long diameter

Since the principal expansion of the left ventricle is dorsad enlargement of this chamber is best seen in the left anterior oblique position (Fig 40*B*) It produces a bulge in the lower posterior contour obliterating the retrocardiac space and overlapping the spine normally clear retrocardiac space is encroached on by the large left atrium or obliterated except for a small triangular area just above the diaphragm At the same time the left main bronchus may be elevated and flattened and the angle of bifurcation of the trachea increased [41, 75] In the left oblique view obliteration of the normal clear area between the upper border of the left atrium and the left main bronchus precedes elevation or obstruction of the latter



Fig 40 *A* Left ventricular enlargement in advanced aortic insufficiency Elongation and elevation of left ventricular contour with increased rounding and displacement to the left
B Same case Left oblique view Posterior bulging of left ventricular contour (arrows) Obliteration of retrocardiac space and encroachment on spine

It is important to distinguish left ventricular enlargement from displacement of the cardiac shadow to the left In normal individuals apparent enlargement of the left ventricle is usually due to a high diaphragm It should also be emphasized that displacement of the left lower cardiac contour to the left may be caused by enlargement of the right ventricle (see below) See also Fig 121 (p 662)

Left Atrium

When the left atrium enlarges, it does so chiefly posteriorly and later to the right However in the posteroanterior view the enlarged left atrium, especially its appendage may cause a straightening of the left border or a prominence of the middle salient (Fig 41*A*) To a variable degree this effect is due also to associated elevation and dilatation of the pulmonary artery The posterior enlargement is most often viewed in the right anterior oblique position (Fig 41*B*) In this view the

Enlargement of the left atrium is more clearly indicated by compression of the esophagus [■, 11, 41] In the posteroanterior view the barium outlined esophagus is abruptly and conspicuously displaced to the right and the stream is partially obstructed (Fig 42) In the right anterior oblique view the normal curve of the left atrium as outlined by the barium containing esophagus, is conspicuously deepened and displaced posteriorly (Fig 41*B*) According to Jacobson et al [35] the left lateral upright view of the chest with the esophagus opacified by barium is superior to the right anterior oblique for the demonstration of left atrial enlargement There is distinct thinning of the barium stream in the esophagus with indentation due to backward displacement of the esophagus by the large left atrium If the left ventricle is enlarged the heart is in contact with the esophagus down to the diaphragm

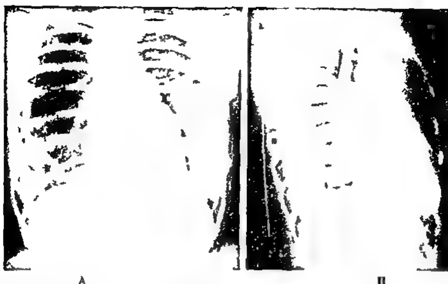


Fig 41 *A* Left atrial enlargement in mitral stenosis Prominent left middle salient due to enlarged left atrial appendage below and elevated pulmonary artery above

B Same case Right oblique view Posterior bulging of enlarged left atrium with diminution of retrocardiac space posterior displacement and compression of barium filled esophagus



Fig 42 Left atrial enlargement in advanced mitral stenosis and heart failure Compression of barium filled esophagus and displacement to the right (lower arrow) Left bronchus (upper arrow) elevated almost to horizontal position by dilated left atrium



Fig 43 Enlarged left atrium in mitral stenosis Globular shadow of hypertrophied left atrium appears as distinct density within cardiac shadow Extends on right beyond right atrial border On upper left it elevates left bronchus

If the left atrium is greatly enlarged its outline in the dorsoventral view appears on the right border (Fig 43) A double right cardiac contour may thus be formed, the upper consisting of the left atrium and the lower of the right atrium With extreme enlargement of the left atrium especially in the so called "giant left atrium," the above abnormalities are exaggerated and the entire right cardiac border is formed by that chamber, which may extend far into the right pulmonary field It may appear also on the left border as a conspicuous segment below the pulmonary artery With pronounced enlargement, the density of the left atrium also increases and its shadow can actually be distinguished within the cardiac shadow (Fig 43)

Right Ventricle

Enlargement is difficult to diagnose in its early stages on the basis of conventional roentgenograms for the enlargement is usually anterior and does not cause the chamber to reach the cardiac borders Whereas Lehman and Curry[48] reported a high degree of accuracy in the roentgen ray evaluation of right ventricular hypertrophy, Sussman and Jacobson[77] concluded that right ventricular enlargement is overdiagnosed radiologically Enlargement of the right ventricle is then recognized by its indirect effects namely elevation and rotation of the pulmonary artery which fills out the waist of the cardiac silhouette and results in straightening of the left border or convex prominence of the pulmonary salient Or the pulmonary artery may form a distinct prominence below the aortic knob (Fig 44) Furthermore the conditions responsible for right ventricular enlargement often cause pulmonary artery dilatation which also accents the left middle cardiac salient With extreme enlargement the pulmonary conus rotates clockwise on the

long axis of the heart and may participate in the left pulmonary salient Since straightening of the left border and prominence of the pulmonary salient occur most often with mitral stenosis, this distinctive configuration has been termed "mitralization" of the heart But in mitral stenosis it is the enlarged left atrial appendage and not the dilated pulmonary artery which forms the major portion of the prominent middle salient

ventricle is increased the notch between it and the left ventricle being displaced posteriorly toward the spine [56] However, doubt has been cast on this localization of the inter ventricular groove by angiocardiographic studies [■] Anteriorly, the lower cardiac border, representing the right ventricle, bulges prominently and may form a conspicuous angulation where it joins the contour of the right atrium above it

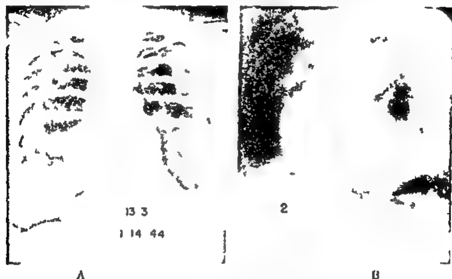


Fig 44 *A* Enlargement of right ventricle Chronic cor pulmonale Prominence and elongation of left middle (pulmonary) segment due to dilated elongated pulmonary artery Right ventricle does not reach cardiac borders in this view In right oblique view enlarged right ventricle bulged anteriorly obliterating retrosternal space
B Angiocardiogram same case Left oblique view Opacification of pulmonary artery with Diodrast shows pronounced dilatation of that vessel

Enlargement of the outflow tract of the right ventricle may be observed in the right anterior oblique as an anterior projection of the lower contour toward the sternum and in lateral views by obliteration of the retro sternal space

When the right ventricle is conspicuously enlarged (in its inflow as well as outflow tracts) it may rotate sufficiently to form most or all of the left cardiac border including the apex of the heart The original apex is elevated by the enlarged right ventricle with a resultant characteristic rounding of the lower left contour (Fig 121) The enlarged right ventricle may displace the right atrium to the right Both of these factors tend to increase significantly the transverse diameter of the heart

Enlargement of the inflow tract is best seen in the left anterior oblique position The diaphragmatic surface formed by the right

Angiocardiography discloses right ventricular hypertrophy by a change in the curvature of the interventricular septum Normally the septum is convex to the right, with right ventricular hypertrophy unaccompanied by left ventricular hypertrophy the septum becomes straightened and later convex to the left

Right Atrium

When the right atrium enlarges it expands chiefly to the right but also upward and posteriorly Roentgenoscopically, its enlargement is denoted in the posteroanterior view by outward displacement of the right lower cardiac contour Displacement to the right may, however, be caused also by enlargement of the right ventricle occasionally and by that of the left ventricle rarely When the displacement reaches the right midclavicular line, the right atrium is definitely enlarged but this is usually part of a generalized cardiac en



Fig 45 Generalized chamber enlargement Mitral aortic and tricuspid valvular disease Right atrium enlarged to right and upward Left atrium extends to both borders

largement or is due to combined mitral, aortic and tricuspid valvular disease (Fig 45) or congenital atrial septal defect

In the right anterior oblique position, the enlarged right atrium encroaches on or obliterates the lowermost portion of the retrocardiac space but it does not displace the esophagus

In the left anterior oblique position, the large right atrium causes a bulge in the upper anterior cardiac segment Enlargement of the right atrium may be simulated not only by enlargement of the ventricles but rarely also by an aneurysm of the ascending aorta reaching down toward the diaphragm by an arteriosclerotic dilated descending aorta and by para-esophageal hernia

ELECTROCARDIOGRAPHIC AND VECTORCARDIOGRAPHIC SIGNS OF CARDIAC ENLARGEMENT

The electrocardiogram may indicate or corroborate the presence of cardiac enlargement The clinical and roentgenologic findings should be considered in making a diagnosis of cardiac enlargement on the basis of the electrocardiogram The electrocardiogram does not reveal uniform, generalized enlargement of the heart but may be characteristically altered by disproportionate enlargement of one of the chambers It may suggest the presence of both left and right ventricular hypertrophy

A number of factors which have been cited above as altering the size and form of the cardiac silhouette likewise alter the form of the electrocardiogram Just as we must distinguish in roentgenograms of cardiac displacement or rotation from somewhat similar ones of cardiac enlargement so we must distinguish the electrocardiographic changes due to cardiac enlargement from those caused by the position or rotation of the heart within the chest [37]

DEVIATION OF THE ELECTRICAL AXIS

The electrical axis (or spatial vector) of the heart may be deviated from its normal direction by rotation of the heart about three axes [3]

1 The *longitudinal axis* (base to apex) One visualizes the heart as if he were facing the apex The heart rotates clockwise or counter clockwise around this axis, the direction being determined by imagining the face of a clock pinned on the apex

2 The *anteroposterior axis* Imagine viewing the anterior surface of the heart and that the face of a clock is pinned on this surface The heart rotates clockwise or counterclockwise about this axis With counterclockwise rotation the position of the heart becomes transverse with clockwise rotation it becomes vertical in the frontal plane

3 The *transverse axis* (left to right) Rotation about this axis brings the apex of the heart anteriorly or posteriorly

The Recognition of Axis Deviation

1 Mean Electrical Axis One means of discovering deviation of the electrical axis from the normal or usual is to determine the vector representing the mean electrical axis of the heart by the Einthoven triangle or triaxial reference system, and note the angle of deviation from the horizontal (see p 36) (Figs 18 19) Normally the electrical axis of the heart is directed downward and to the subject s left making an angle of 0° to 90° with the horizontal When the electrical axis is rotated counterclockwise or to the left, the angle of deviation becomes negative when the electrical axis is rotated clockwise or to the right the angle of deviation becomes more than 90° In infancy the electrical axis is greatly deviated to the right (100° to 150°) [62]

2 Vectorcardiogram Deviation of the electrical axis may also be recognized from the frontal plane projection of the vectorcardiogram Left axis deviation is disclosed by a counterclockwise loop with its long axis making an angle between 0 and minus 90° with the horizontal Right axis deviation is indicated by clockwise inscription of the QRS loop with its long axis beyond + 90° Furthermore careful observation of the spatial position of the initial and terminal vectors of the QRS loop and of the width of the loop in each portion reveals the position and type of rotation of the heart and aids in differentiating rotation of the heart from right and left ventricular hypertrophy, bundle branch block and myocardial infarction [89]

3 Ventricular Gradient (p 51) In normal subjects the direction of the ventricular gradient is within the range of 0° to 90° from the horizontal deviates not more than 20° to either side of the anatomic (longitudinal) axis of the heart (H) and deviates not more than 20° to 25° to the right nor more than 35 to the left of the vector $\hat{A}_{QRS}$ In left deviation of the electrical axis the axis of $\hat{G}$ is rotated to the left so that it tends to the transverse position Furthermore it deviates further to the left than H but less than $\hat{A}_{QRS}$ With right axis deviation $\hat{G}$ becomes vertical, both $\hat{G}$ and $\hat{A}_{QRS}$ are rotated to the right of the anatomic axis of the heart (H) but $\hat{A}_{QRS}$ is rotated more than $\hat{G}$

4 Direct Inspection of Q R and S in Standard Leads *Normally the electrical* axis has been noted to be directed downward and to the subject's left at any angle of 0° to 90° with the horizontal As the heart is rotated to the left or counterclockwise on its anteroposterior axis its mean electrical axis becomes more nearly parallel to the lead I line in the triaxial reference system and more nearly perpendicular to lead III Therefore the positive voltage in lead I, represented by R_1 becomes higher and the voltage in lead III represented by R_3 becomes lower When the rotation of the electrical axis to the left (or counterclockwise) is so great that it is directed to the subject s left and upward, the angle with the horizontal becomes negative and the maximal voltage in lead III diminishes below 0° and becomes reversed This is indicated by an inverted major deflection or a deep S_3 while R_1 remains tall Electrocardiographic curves with a tall R wave in lead I (taller than R_2) and a deep S wave in lead III are said to show *left axis deviation* (Fig 19A) A Q_1 is often present but no Q_3 T_3 may be inverted and occasionally P_3

As the electrical axis of the heart is shifted to the right or clockwise, it becomes more nearly parallel to lead III and more nearly perpendicular to lead I The maximal voltage in lead III and therefore the R wave in that lead become higher while the voltage and R wave in lead I become lower As the electrical axis comes to be directed downward and to the subject's right (instead of to the left as is normal), the angle with the horizontal ex

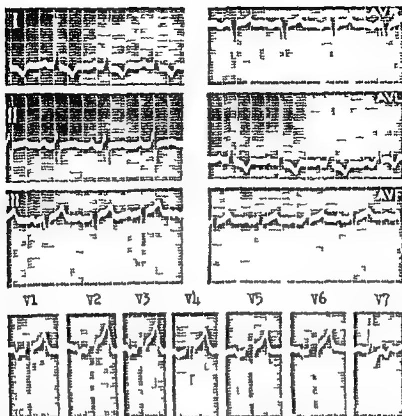


Fig 46 Enlargement of the left ventricle (left ventricular strain) Tall R_1 dominant R_1 with deep S_3 ST slightly depressed and T inverted in standard leads Small R in V_1 and deep S in right precordial leads Tall R delayed peak of R and inverted T in V_6 over left ventricle Counterclockwise rotation (horizontal heart) shown in unipolar limb leads by negative major deflection in left leg lead (aVF) and high R in left arm lead (aVL)

ceeds 90 degrees the voltage diminishes below 0 in lead I and becomes negative and the main electrocardiographic deflection is inverted Thus there is a deep S_1 while R_3 is tall (Fig 47) Electrocardiograms with a tall R_3 (taller than R_1) and a deep S_1 are described as showing *right axis deviation* There may be a Q_3 but no Q_1 T_1 and P_1 may be of low voltage or inverted

The simplest and most practical way of determining the presence of left or right axis deviation is by inspection The degree of axis deviation can be roughly evaluated by noting the height or depth of the R and S waves Thus the taller R_1 and the deeper S_3 are the greater the degree of left axis deviation and the taller R_3 and the deeper S_1 are the greater the degree of right axis deviation

5 **Unipolar Limb Leads** The features of the electrocardiogram associated with an horizontal semihorizontal vertical semivertical and intermediate position of the heart are indicated essentially by the unipolar limb leads aVL and aVF as shown in Table 1 It should be stressed that the terms vertical horizontal etc refer to position of the electrical axis and not to the anatomic position of the heart however there may be a close correlation when other modifying factors are absent

The findings in the unipolar limb and precordial leads with various cardiac positions are explained by the assumptions that the left arm electrode (and V_{5-6}) face the epicardial surface and the oncoming activation wave of the left ventricle most directly when the heart is transverse and that the left leg electrode (and V_7) face them most directly when the heart is vertical Since the dominant electromotive forces are determined by the left ventricle and a predominantly positive wave is inscribed when the activation wave approaches the recording electrode the major deflection is upward in the left arm lead (aVL) and V_{5-6} when the heart is transverse

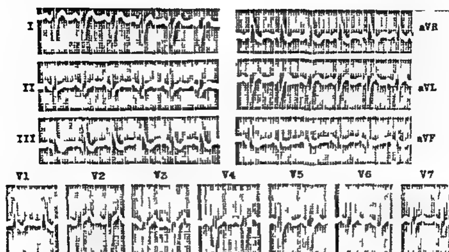


Fig 47 Enlargement of right ventricle (right ventricular strain) R_3 taller than R and deep S_1 in standard leads R tall and larger than S and T inverted in V and aVR Unipolar limb leads show upright major deflection in aVR resembling aVF with inverted major deflection in aVL indicating vertical position or clockwise rotation of the heart

and upward in the left leg electrode (aVF) *when the heart is vertical Actually there is* recorded the typical left ventricular complex Rs or qRs in the left arm lead when the heart is horizontal and in the left leg lead when the heart is vertical (Fig 47) Conversely in the horizontal heart the left leg electrode (aVF) and V_1 face the right ventricular epicardium and oncoming initial septal and right ventricular activation wave and the so-called right ventricular complex rS is recorded Or *else the predominant downward deflection is* explained as due to the electrode facing the negative side of the dominant left ventricular activation wave According to vectorcardiographic theory, the different patterns are explained not by proximity of an electrode to one or the other cardiac chambers but as the result of a change in the direction and magnitude of the spatial vector of all the electromotive forces of both ventricles when the *orientation of the heart is altered*

The Electrical Axis in Relation to Anatomic Axis of the Heart and Body Build

There is a fairly good but imperfect relationship between the electrical and the anatomic (longitudinal) axis (H) of the heart [19] The direction of the electrical axis like that of the anatomic is downward and to the left Furthermore counterclockwise rotation of the electrical axis in the frontal or horizontal plane i e deviation to the left usually accompanies a counterclockwise or leftward rotation of the heart on its longitudinal or anteroposterior axis i e a transverse position of the heart Similarly, clockwise rotation of the electrical axis (deviation to the right) usually accompanies clockwise rotation of the heart or a vertical position

Deviations in the electrical axis of the heart may be quantitatively more extensive than changes in the anatomic axis [27] It would lead to absurdity to attempt to localize the anatomic *axis in the direction and vicinity of the*

Table 1 Identifying Electrocardiographic Characteristics of Electrical Position of the Heart

	HORIZONTAL	SEMIHORIZONTAL	VERTICAL	SEMIVERTICAL	INTERMEDIATE
aVL	Tall R No S Similar to V_6	Medium R No S Similar to V_6	Small R Deep S Similar to V_1	Small R Small S	Small R No S Similar to V_6
aVF	Small R Deep S Similar to V_1	Small R Small S	Tall R No S Similar to V_6	Medium R No S Similar to V_6	Small R No S Similar to V_6

electrical axis when the deviation of the latter is extreme for example beyond plus 100° or beyond minus 30 As we shall see the electrical axis is determined by other factors besides the anatomic position of the heart in the thorax

Howard and Gertler[34] attempted to correlate the deviation of the electrical axis with body build as classified by Sheldon s method of somatotyping[11] The latter based on anthropometry and regarded as the most satisfactory index for expressing body build classifies body build into endomorphy ectomorphy and mesomorphy Left (electrical) axis deviation was correlated with endomorphy, right axis deviation with ectomorphy With increasing obesity (not muscularity) and compactness of the body there was a greater tendency to leftward deviation of the electrical axis, with more linear build to right axis deviation On the other hand the correlation of axis deviation with weight, chest width and the ratio of height to cube root of weight (the ponderal index) was only slightly significant

Axis Deviation Due to Positional Change or Cardiac Enlargement

The electrocardiographic changes associated with deviation of the electrical axis to the left or right have sometimes been described as denoting left ventricular or right ventricular preponderance i e they were presumed to indicate disproportionate hypertrophy or enlargement of the left or right ventricle[50] Indeed left and right ventricular enlargement are common causes of pronounced left or right axis deviation but the patterns of the latter are often produced in the absence of cardiac enlargement[65] and in fact right axis deviation may occasionally be encountered in a heart with left ventricular enlargement[86]

The electrocardiographic pattern of left axis deviation of moderate degree (0 to minus 20) is normally observed in the constitutionally sthenic person with a transversely situated heart in obese subjects with a high diaphragm and in pregnant women It occurs in association with ascites After a maximal expiration left axis deviation is accentuated i e R is increased in lead I diminished in lead III and the height of T increases in leads I and II and in the precordial leads[45] When the electrical axis is more markedly deviated to the left (i e when the angle alpha made with the horizontal axis is beyond minus 20°, and especially beyond minus 30°), it is usually indicative of myocardial disease

Dilatation and hypertrophy of the left ventricle and left bundle branch block are usually associated with left axis deviation, which may be marked Left ventricular enlargement may modify the electrical axis both by rotating the heart and by modifying the direction and magnitude of the electromotive forces generated by the heart Bundle branch block modifies the apparent electrical axis by altering the development of potential variations in the two ventricles

The electrocardiographic pattern of right axis deviation of moderate grade (plus 90° to 100°) is normally observed in asthenic individuals with centrally situated vertical or drop heart and in early infancy It is commonly observed in pulmonary emphysema and a low diaphragm After a deep inspiration right axis deviation may be produced or accentuated especially in the standing position R decreases in lead I, and T decreases or may become slightly negative[45] A shift of the mediastinum and heart to the left tends to produce right axis deviation A marked right axis deviation (beyond 110° to 120) usually denotes myocardial disease and is not due to positional change alone but it may be observed in the normal infant less than six months old[53] Right axis deviation is commonly associated with right ventricular dilatation and hypertrophy and with right bundle branch block and may be of marked degree

THE ELECTROCARDIOGRAM IN HYPERTROPHY OF THE LEFT VENTRICLE (LEFT VENTRICULAR STRAIN)

Certain electrocardiographic changes have been correlated empirically with left ventricular hypertrophy although one or more of the stated electrocardiographic criteria may be absent in proven cases of hypertrophy of the left ventricle[68, 154] The observed electrocardiographic changes are explained on the basis of an hypertrophied thickened free wall of the left ventricle Hence (1) greater electromotive forces are generated the R wave is taller in electrodes facing the epicardial surface of the left ventricle (V_5 and V_6) and in electrodes facing the negative aspect of the activation wave of the left ventricle (V_1 and V_2) there is a deep S wave (2) a longer period is required for the activation wave to travel from the endocardial to the epicardial surface of the

thickened left ventricle and therefore the duration of the QRS may be slightly increased, (3) for the same reason the time of arrival of the activation wave at the region underlying left precordial electrodes (V_5 and V_6) is delayed i e , the intrinsicoid deflection is delayed

When there is a marked increase in the electromotive forces associated with depolarization of the hypertrophied left ventricle there is a secondary and similar increase in the forces of repolarization Thus the leads showing very tall R waves may also disclose a depressed S T segment and inverted T waves since the greater the area of the positive depolarization complex (QRS) the greater the area of the negative repolarization complex (S T and T) In the absence of myocardial disease the ventricular gradient is unaltered in ventricular hypertrophy Hence the positive forces of the ventricular gradient may not be sufficient to overcome the increased negative forces of repolarization of the hypertrophied ventricle the T wave is therefore negative and the S T segment may be depressed The negative T wave is a secondary T wave change (p 51)

The following electrocardiographic changes are usually observed in conditions associated with isolated or predominant left ventricular hypertrophy (in hypertensive heart aortic valvular heart disease coronary heart disease with left ventricular failure, congenital subaortic stenosis or tricuspid atresia) (Fig 48*B*)

1 *Multiple unipolar precordial leads* provide the most reliable evidence of left ventricular hypertrophy [17]

(a) The R wave in V_5 and V_6 overlying the hypertrophied left ventricle is of high voltage and there is usually a Q wave of moderate depth R in V_5 exceeds 26 mm and R in V_5 plus S in V_1 exceed 35 mm [31]

(b) There is a deep S in leads V_1 and V_2 and perhaps in V_3 but the R wave is small or minute in these leads

(c) The transition point at which R becomes as high as or higher than S shifts from about V_3 to V_2 or V_1 when there is counterclockwise rotation, or to V_4 or V_5 when there is clockwise rotation

(d) The peak of the R wave, or presumed onset of the intrinsicoid deflection in leads $V_{5,6}$ occurs relatively late in the QRS interval, i e the interval from the beginning of the QRS to the peak of R is 0 05 second or more instead of the normal maximum of 0 035 second in left precordial leads The intrinsicoid deflection occurs normally in the right precordial leads V_1 and V_2 (about 0 01 to 0 02 second after the onset of the QRS)

(e) The QRS interval in left precordial leads may be slightly prolonged to 0 10 or even 0 11 instead of a normal duration of about 0 08 second

(f) The T wave in left precordial leads is blunted and low or becomes inverted The S-T segment is depressed in the same leads According to Wood and Selzer [31] left axis deviation without left ventricular hypertrophy may be associated with inversion of the T wave in V_3 and occasionally in V_4 but not in V_5 In right precordial leads (V_1, V_2) the S T segment is often slightly elevated and the T wave upright and tall in left ventricular hypertrophy

2 The electrocardiographic changes *in the unipolar limb leads* vary somewhat according to the position of the heart

(a) There is increased voltage of the R wave (more than 11 mm) widening of the QRS to 0 10–0 11 mm and delayed intrinsicoid deflection in the lead facing the left ventricle, usually aVL

(b) The S T segment is depressed and the T wave inverted in the lead with the tall R usually aVL

(c) When the position of the heart is vertical and the electrical axis is deviated to the right the left ventricle faces the left leg (aVF) and a tall R, depressed S T and inverted T wave are observed in aVF

3 *In the standard limb leads,*

(a) There is usually *left axis deviation* S_3 is of greater amplitude than R_3 R_1 is taller than R_2 or R_3 This is particularly suggestive of left ventricular hypertrophy if left axis deviation is pronounced (the axis is located between minus 20° and minus 60°)

(b) *R_1 or S_3 or both may have an abnormally high voltage* (above 1 7 mv) Or the sum of R_1 and S_3 exceeds 2 4 mv (24 mm)

(c) *S T_1 is depressed and S-T_3 may be slightly elevated T_1 is very low or inverted and T_2 may also be low or inverted* In cases of left axis deviation due to rotation with transverse position of the heart but without hypertrophy, there may be inversion of the T wave in lead III but not in lead I [28]

(d) When the heart has a vertical position there may be a normal electrical axis or right

axis deviation despite the development of left ventricular hypertrophy [1, 74] The presence of left ventricular hypertrophy is then indicated in the precordial leads, while the position of the heart is disclosed by the unipolar limb leads When left ventricular hypertrophy is associated with a normal electrical axis the T waves may be inverted in leads I II and III, or when it is associated with right axis deviation (S_1 prominent and R_3 larger than R_1) the T waves are inverted in leads II and III Whereas Q waves are often present in lead I when there is left axis deviation with hypertrophy, Q waves are present in leads II and III when the electrical axis is normally situated or deviated to the right

Left ventricular hypertrophy is distinguished from left axis deviation without hypertrophy by the high voltage of the R, delayed onset in R peak, S T depression and inversion of T wave in left precordial leads Its electrocardiographic differentiation from left bundle branch block (p 398) may be difficult Essentially it depends on the greater prolongation of the QRS and later onset of intrinsicoid deflection with bundle branch block Sometimes left ventricular hypertrophy is associated with an electrocardiogram simulating that of myocardial infarction and conversely myocardial infarction may be associated with the electrocardiographic pattern of left ventricular hypertrophy (p 527)

THE VECTORCARDIOGRAM IN LEFT VENTRICULAR HYPERTROPHY

The following vectorcardiographic changes are observed in left ventricular hypertrophy by the cube method of Grishman[12]

The *direction* of inscription of the QRS loop is normal namely counterclockwise in the horizontal projection, clockwise in the sagittal and usually counterclockwise in the frontal But in vertical hearts the direction of inscription may be clockwise in the frontal plane projection

The QRS vector loops are oriented more posteriorly and more to the left than in normal hearts (Fig 48)

The long axis of the QRS loop lies usually between minus 30 and minus 50 in the horizontal plane projection and between plus 5° and plus 40 in the frontal plane

The QRS loop may not be closed prior to inscription of the T loop (corresponding to ST segment deviation) The *orientation of the T loop* is altered the loop lying in a segment opposite the QRS loop, and the axis of the T loop forming approximately a 180° angle with the axis of the QRS loop This corresponds in the electrocardiogram with T waves directed opposite to the major deflection of the QRS Occasionally the QRS fails to close prior to inscription of the T loop corresponding to the RST depression in the electrocardiogram

THE ELECTROCARDIOGRAM IN RIGHT VENTRICULAR HYPERTROPHY

Genesis of Electrocardiographic Pattern

Two possible factors appear to be concerned in the genesis of the electrocardiographic pattern associated with right ventricular hypertrophy (1) hypertrophy of the muscle fibers and consequent thickening of the right ventricular wall, and (2) clockwise rotation of the heart as the right ventricle enlarges anteriorly and to the left

Clockwise Rotation Theory According to one theory which is based chiefly on studies with intracardiac leads and direct leads at operation the electrocardiographic pattern in right ventricular hypertrophy is determined by extreme clockwise rotation of the heart so that the posterobasal portion of the left ventricle faces the right precordial leads V_{3R}, V_E and V_1 [44, 88] while the right ventricular epicardium faces the electrodes situated at V_2 or V_3 to V_4 Thus tall R waves in V_1 V_E and V_{3R} are produced by electromotive forces generated by the rotated left ventricle and not by the thickened right ventricle The rS pattern in precordial leads further to the left (V_2 to V_6) is attributed to rotation of the hypertrophied right ventricle, which has come to lie beneath the left precordial electrodes The r of the rS is the representation of initial septal and right ventricular activation whereas the S preresents the left ventricular activation wave which is now traveling *away* from the left precordial electrodes

In the normal heart and in left ventricular hypertrophy, Q waves are often present in left precordial leads but not in those on the right (V_1), because of initial septal activation from left to right In right ventricular hypertrophy, Q waves are frequent in *right precordial leads* not left This also accords with the rotation theory since the septal activation wave from left to right would now be directed

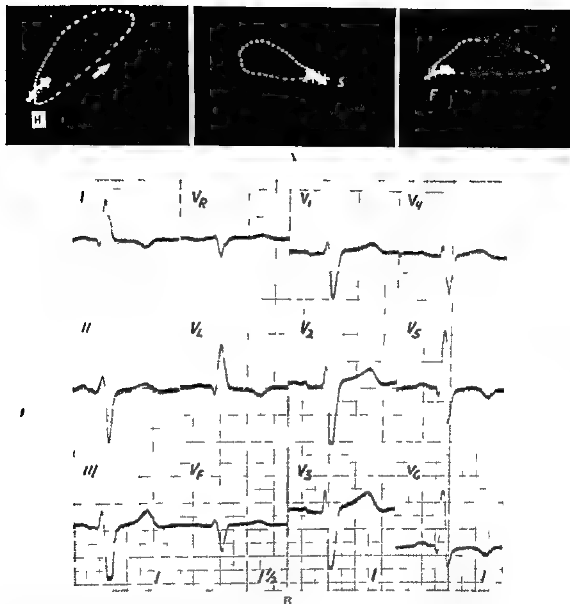


Fig 48 4 Vectorcardiogram indicating left ventricular hypertrophy in a 62 year old subject H horizontal S sagittal F frontal plane projections Counterclockwise in horizontal plane Vectorcardiographic loop is directed posteriorly to the left and superiorly
B Electrocardiogram in same case at 50 mm per second

toward left precordial leads over the right ventricle where a positive wave is inscribed, and away from right precordial leads over lying the left ventricle, where a negative (Q) wave is inscribed [21]

Other findings in right ventricular hypertrophy are also in harmony with the theory of rotation, according to which a left ventricular activation pattern (Rs or qR) is observed in right precordial leads (e g V_1) and a right ventricular pattern (rS) in left precordial leads (e g, V_5 V_6) Thus there is no widening of the QRS complex in right precordial leads because the underlying left ventricle is not hypertrophied The delay in onset of the intrinsicoid deflection in right precordial leads to about 0 04 second instead of 0 02 second is interpreted not as a delay in right ventricular intrinsicoid deflection but as the normal onset of the intrinsicoid deflection in the underlying left ventricle

One important objection to this hypothesis is the observation that the T wave is often inverted (and the S T segment depressed) in

right precordial leads, which, according to the rotation theory, reflect left ventricular activity But since the left ventricle is usually normal there is no reason for these ST and T wave changes

Increased Right Ventricular Potentials The other theory regarding the genesis of the electrocardiogram in right ventricular hypertrophy attributes the changes chiefly to the hypertrophy of the right ventricle per se in consequence of which greater electromotive forces are generated, sufficient to dominate those of the left ventricle Therefore, tall R waves larger than S are recorded in right precordial leads over the right ventricle The delay in onset of R peak is explained by the longer time it takes for the activation wave to travel from endocardium to epicardium of the thickened right ventricular wall ST T wave negativity is secondary to an increase in the voltage and sometimes to the duration of depolarization of the hypertrophied right ventricle Other changes are due to clockwise rotation of the heart but the latter is not primarily responsible for the findings in right precordial leads The electrocardiographic changes of right ventricular hypertrophy have also been well correlated with increased pulmonary resistance increased pulmonary arterial and right ventricular pressures[46, [illegible], 47] but the manner in which such pressure elevations produce the electrocardiographic alterations is not clear

The chief objection to this explanation of the electrocardiographic pattern is that the right ventricle even when hypertrophied is much thinner than the left ventricle except possibly in some cases of mitral stenosis with left ventricular atrophy and some cases of congenital heart disease It is therefore difficult to explain either dominance of right ventricular over left ventricular forces or more particularly the greater delay in onset of intrinsicoid deflection in right precordial leads (V_1) than in left (V_6) if the former represents the activation wave through the thinner, though hypertrophied right ventricle

Vectorcardiographic Theory By this theory in contrast to the theory that recorded potentials are dependent on proximity of the precordial electrode to the right or left ventricle the electrocardiographic pattern of right ventricular hypertrophy is not determined by the thickness of the hypertrophied chamber wall or by the exact relation of a given electrode to the right or left ventricle Rather it is determined by the effect of hypertrophy and rotation on the summation of spatial vectors of combined ventricular activity from moment to moment

The Electrocardiographic Pattern of Right Ventricular Hypertrophy

In many cases of right ventricular hypertrophy especially in most cases secondary to chronic pulmonary disease the degree of hypertrophy is slight and its effect on the electrocardiogram insignificant [illegible] This is presumed to be due to the preponderant effect of left ventricular forces even when the right ventricle is somewhat hypertrophied The electrocardiogram may appear normal or show only a vertical position On the other hand when the electrocardiogram does show a pattern of right ventricular hypertrophy, the latter will usually be confirmed at autopsy [illegible] The electrocardiogram may be of particular value in confirming the diagnosis of right ventricular hypertrophy in congenital heart disease, in which the most extreme grades of hypertrophy are found especially in interatrial septal defect pulmonary stenosis tetralogy of Fallot and pulmonary arteriolar disease [illegible]

The following electrocardiographic changes may be associated with right ventricular hypertrophy (Figs 47 and 49*B*)

1 **The Precordial Leads** (a) There is a tall R (more than 0 7 mv or 7 mm) in right precordial leads (V_1 and/or V_{3R} or V_E) Peak of R is delayed to more than 0 03 after onset of the initial complex Q is often present giving a qR complex S is absent ST may be depressed and T inverted in these right precordial leads

(b) In left precordial leads (V_5 and V_6) there is a small r and a deep S (rS pattern) R peak occurs earlier than in V_1

(c) Another pattern is characterized by a tall R with delayed peak and a small s in right precordial leads resulting in an R/S ratio of greater than 1 [illegible] The R/S ratio falls progressively from right to left precordial leads and there is a deep S in V_5 and V_6

(d) With severe right ventricular hypertrophy especially in congenital heart disease, there may be an rsR′ pattern in right precordial leads, with high voltage and delayed

peak of the R′, left precordial leads show a wide S The appearance is that of an incomplete bundle branch block [7a, 7b]

2 Unipolar Limb Leads (a) aVR shows a qR or a QR pattern with the height of R more than 5 mm (0 5 mv) and R/Q ratio greater than 1 T is inverted Occasionally there is an rSR′ pattern

(b) The other unipolar leads show varying patterns depending on positional changes Usually there is a qR pattern and inverted T in aVF and an RS pattern in aVL with upright T

3 Standard Limb Leads (a) *Right axis deviation* S_1 is of greater amplitude than R_1 R_3 is taller than R_1 or R_2 This is suggestive of right ventricular hypertrophy if the axis deviation is pronounced (mean electrical axis beyond plus 110° to 120° and S_2 deep)

(b) R_3 and S_1 may have abnormally high voltage This finding increases the probability that right axis deviation is due to right ventricular hypertrophy

(c) T_2 and T_3 are inverted and ST_2 and ST_3 are depressed The combination of these ST T changes with right axis deviation forms the pattern of so called "right ventricular strain," often regarded as diagnostic of right ventricular hypertrophy [3] But there are exceptions [17, 24]

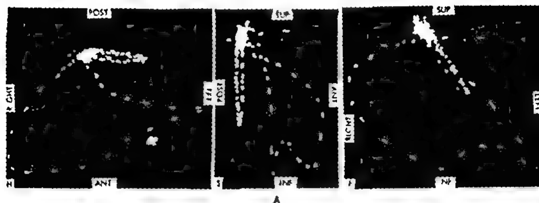
4 Tall or widened P waves in association merely with a vertical electrical position of the heart or in combination with the above more distinctive changes, are often observed in right ventricular hypertrophy

Donzelot et al [14] correlated a variety of electrocardiographic patterns with specific congenital cardiac lesions Tetralogy of Fallot was usually associated with an 'adaptation' pattern characterized by an inverted QRS and a slightly elevated ST segment in lead I, upright T waves in II and III tall R in V_1 and V_{3R} and aVR, and upright T waves in V_5 and V_6 Interatrial septal defect was usually associated with the 'surcharge' pattern characterized by incomplete bundle branch block (rR′ in V_1 and V_{3R}) Pulmonary stenosis was usually associated with the "barrage" pattern characterized by ST depressions and T wave inversions in leads II, III, V_1 V_5 and aVF and by an inverted QRS slightly elevated ST and upright T in leads I and aVL Cabrera and Monroy,[7] and Sodi Pallares and Marsico [72] described similar patterns, which they related to systolic or diastolic overloading Systolic overloading of the right ventricle, e g, in pulmonic stenosis was associated with tall R waves and inverted T waves in right precordial leads Diastolic overloading, e g, in interatrial septal defect, was associated with incomplete or complete right bundle branch block

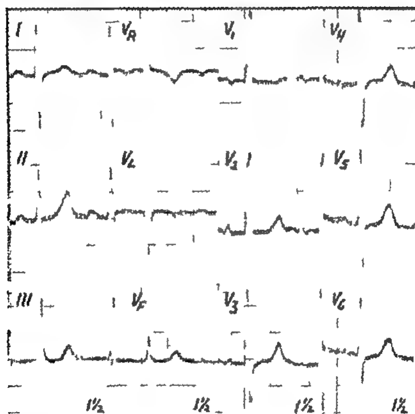
The electrocardiographic pattern of right ventricular hypertrophy must be distinguished from that of right axis deviation due to positional change without hypertrophy from that of right bundle branch block and from that of certain instances of myocardial infarction Delay in onset of the intrinsicoid deflection (peak of R wave) in right precordial leads R taller than 7 mm in V_1 or taller than 5 mm in lead aVr and mean electrical axis beyond plus 110° to plus 120° all indicate right ventricular hypertrophy rather than mere rotation without hypertrophy Right bundle branch block is discussed on page 399 The QRS complex in V_1 is of normal duration in right ventricular hypertrophy prolonged to 0 11 or 0 12 in incomplete block or to 0 13 second or more in complete right bundle branch block But there are exceptions to this rule of differentiation Occasionally incomplete bundle branch block is associated with right ventricular hypertrophy notably in congenital cardiac lesions the presence of hypertrophy as well as branch block is suggested by the tall R waves in V_1 and aVr The differentiation from acute myocardial infarction is discussed on page 521

THE VECTORCARDIOGRAM IN RIGHT VENTRICULAR HYPERTROPHY

The vectorcardiographic patterns differ with the reference system employed Lasser et al [44] using Grishman's cube method of electrode placement observed three distinct five vectorcardiographic patterns, depending on the degree of right ventricular hypertrophy, in cases of congenital heart disease in which an rsR′ pattern occurred in right precordial leads of the electrocardiogram The QRS vector loops were oriented mostly to the right and anteriorly (Fig 49) With increased degree of hypertrophy the loops tended to deviate superiorly and posteriorly This orientation accounts for the occurrence of tall R waves in right precordial leads and in aVr Sometimes the initial component of the QRS loop is inscribed posteriorly and to the left [20] The direction of inscription of the QRS



A



B

Fig 43 *A* Vectorcardiogram indicating right ventricular hypertrophy in a 4 year old girl with tetralogy of Fallot The QRS loop in the horizontal projection is inscribed clockwise The vectorcardiogram is directed inferiorly anteriorly and to the right

B Electrocardiogram in the same case at 50 mm per second

loop is often altered notably a clockwise inscription in the horizontal plane projection instead of the normal counterclockwise[23] The T and QRS loops are divergent accounting for inverted T waves in leads with a predominant upright QRS complex Flek et al[15] observed similar vectorcardiographic changes in mitral stenosis as well as in congenital heart disease Richman and Wolff[6] also described in detail characteristic and diagnostic vectorcardiographic patterns in right ventricular hypertrophy

Certain advantages have been claimed for vectorcardiography over electrocardiography

in the diagnosis of right ventricular hypertrophy.[13] The vectorcardiogram may demonstrate that there is no right ventricular hypertrophy when electrocardiograms suggest its presence, especially in normal subjects with a thin chest wall. Or the vectorcardiogram may indicate right ventricular hypertrophy when this is not diagnosed from the electrocardiogram. It is uncertain whether the latter possible deficiency is due to inadequate leads or a failure in proper analysis of the electrocardiogram.

The vectorcardiogram is said to enable differentiation of right ventricular hypertrophy from right axis deviation without hypertrophy, from incomplete bundle branch block and from myocardial infarction, when such differentiation may be difficult or impossible by electrocardiography. The right axis deviation observed normally in infants and young children usually may be distinguished from that due to right ventricular hypertrophy by the normal direction of inscription and normal general configuration of the QRS loop in the former.[47] Lasser et al.[48] differentiated right ventricular hypertrophy from incomplete bundle branch block in cases with an rSR′ electrocardiogram in right precordial leads. In right ventricular hypertrophy the orientation and inscription of the QRS loop are abnormal, but the terminal segment is inscribed with normal velocity. In bundle branch block the initial segment of the QRS loop is inscribed *normally, but there is* an additional terminal appendage directed anteriorly and to the right, with its angular velocity reduced so that the time markings are close together (p. 401).

THE ELECTROCARDIOGRAM IN COMBINED VENTRICULAR HYPERTROPHY

Hypertrophy of both ventricles may occur, notably in combined mitral stenosis and aortic valvular lesions and with the coexistence of diseases causing left and right ventricular hypertrophy, e.g., hypertension and cor pulmonale. Usually there is predominant hypertrophy of either the right or left ventricle and the electrocardiographic pattern is determined by that predominance but often the presence of both obscures the electrocardiographic pattern of either.[51] Pagnoni and Goodwin[53] studied the unipolar lead electrocardiograms in 51 cases of combined ventricular hypertrophy confirmed at autopsy. In 13 there were electrocardiographic signs of left ventricular hypertrophy only, in 10 of right ventricular hypertrophy, in 4 of left bundle branch block, in 2 of right bundle branch block, in 8 non specific changes, and in 13 changes regarded as indicative of combined ventricular hypertrophy. The most suggestive feature was the association of changes denoting a vertical heart (p. 110) with concomitant evidence of left ventricular hypertrophy, e.g., delay in peak of R wave in V_5 to more than 0.05 second, and ST segment depression and T wave inversion in V_5. Another combination suggesting combined ventricular hypertrophy included the above evidence of left ventricular hypertrophy, together with S greater than r in V_5 or R greater than q in aVr and an enlarged P in V_1, or inverted T in V_1 in adults, signs usually associated with right ventricular hypertrophy.

THE VECTORCARDIOGRAM IN COMBINED VENTRICULAR HYPERTROPHY

Whipple and Levine[44] described a vectorcardiographic pattern which appeared to be closely related to combined ventricular hypertrophy as seen in 8 patients whose hearts were examined at autopsy. The characteristic feature was a very narrow loop (length at least six times that of depth) in the horizontal plane (cube method). The loop was directed to the left and not more than 20° posteriorly. The electrocardiograms had shown probable *combined ventricular hypertrophy in 3 of the* 8 cases, left ventricular hypertrophy in a vertical heart in 2, left ventricular hypertrophy in 1, possible left ventricular hypertrophy in 1, and right ventricular hypertrophy with a delayed intrinsicoid deflection over the left precordium in 1.

THE ELECTROCARDIOGRAM IN ENLARGEMENT OF THE ATRIA

Enlargement of the atria may produce electrocardiographic changes because of hypertrophy of the wall, dilatation of the chambers, rotation of the electrical axis in the course of enlargement, or disease of the atrial wall. The electrocardiographic changes observed include notching of the P waves, and increase in their amplitude or in their duration. According to rigid criteria, the amplitude of the P wave is abnormally increased if its height, measured in one direction from the isoelectric level, exceeds 3 mm. (0.3mv.) in any

standard bipolar extremity lead, or 2 5 mm in any precordial or augmented unipolar extremity lead As a rule, however, P is abnormally tall if it exceeds 2 5 mm in lead II 2 mm in lead I, 2 mm in any precordial lead or 1 5 mm in any augmented unipolar extremity lead P is wide if it exceeds 0 10 second in any extremity lead An abnormally high amplitude has been attributed to hypertrophy with consequent increase in the generated electromotive forces and widening of waves in leads II and III and aVF Right atrial enlargement has been associated with large biphasic waves with a prominent intrinsicoid deflection in right precordial leads V_1 or V_2 and V_3 [75, 17] On the other hand there is evidence that no intrinsicoid deflection of the right atrium can be obtained by available electrode placements because of the distance of the electrode from the surface of the right atrium Therefore it is believed that precordial leads with large biphasic P waves

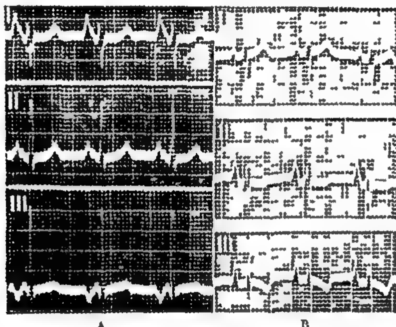


Fig 50 4 (Left) atrial enlargement in mitral stenosis P waves tall notched and widened in leads I and II Right ventricular strain
B (Right) atrial enlargement in chronic cor pulmonale secondary to asthma and obstructive emphysema P waves tall and pointed (peaked) in leads II and III but not widened Right ventricular strain or right axis deviation

the P to dilatation of the atria with consequent prolongation of the depolarizing process or to disease within the wall Notching has been related either to irregularly distributed areas of disease to unequal dilatation of the left and right atria (usually predominantly or exclusively the left) or most probably to a delayed intrinsicoid deflection in left atrial leads

Atrial activity may be best disclosed by esophageal leads or right parasternal leads [78, 8] Left atrial enlargement is most likely to be associated with widening and notching of the P waves usually in leads I and II and in aVL and aVR whereas right atrial enlargement is usually characterized by tall, narrow, peaked in V_1 represent late activation of the *left* atrium and indicate hypertrophy of that chamber [80]

Broad notched and frequently tall P waves usually in leads I and II have been described as mitral P waves and have been associated with mitral stenosis[85, 79] (Figs 50*A*, 51*B*) According to Berliner and Master [4] notching of the P wave occurs in uncomplicated mitral stenosis but broad P waves of very high amplitude are usually found when tricuspid disease is also associated Enlargement of the right atrium secondary to chronic pulmonary disease has been characterized by tall sharply peaked P waves in leads II and III and in aVF (pulmonary P waves) (Figs 50*B*,

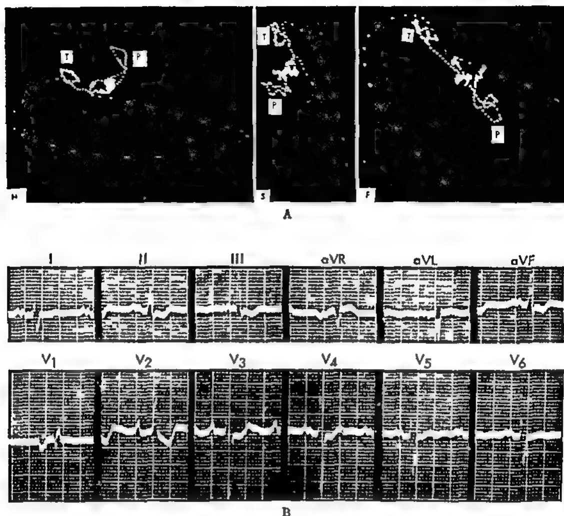


Fig 51 *A* Vectorcardiogram indicating left atrial enlargement The P loop is directed mainly posteriorly and somewhat to the left inferiorly
B Electrocardiogram in same case

52*B*) [40, 68, 71] This type of pulmonary P wave may be observed in normal hearts owing to a vertical position of the heart with forward displacement of the apex perhaps related to an associated low diaphragm and pulmonary emphysema [11] The tall pulmonary P waves may be observed transiently as when they appear during an attack of bronchial asthma and disappear after the attack subsides [9] Observations such as these as well as the lack of correlation of pulmonary P" waves with right atrial hypertrophy [9] tend to support the assumption that "pulmonary P waves are the result of cardiac rotation possibly causing atrial electromotive forces to be directed backward and toward the left leg

In congenital heart disease there is frequently an elevated P wave, maximal in lead II, without widening especially in conditions associated with right atrial enlargement as interatrial septal defect pulmonary stenosis, tetralogy of Fallot and tricuspid stenosis or atresia

In a recent study of the P wave in CR precordial leads, Thomas and Dejong[79] classified the major normal P wave patterns and described distinctive P wave changes in right and left atrial hypertrophy Right atrial hypertrophy was characterized by a tall (more than 2 5 mm) diphasic pointed or bifid P wave in right precordial leads When bifid or notched the first peak (representing right atrial activity) was taller Left atrial hypertrophy was characterized by a tall (more than 3 mm) bifid P wave with the second peak most prominent, in left precordial leads,

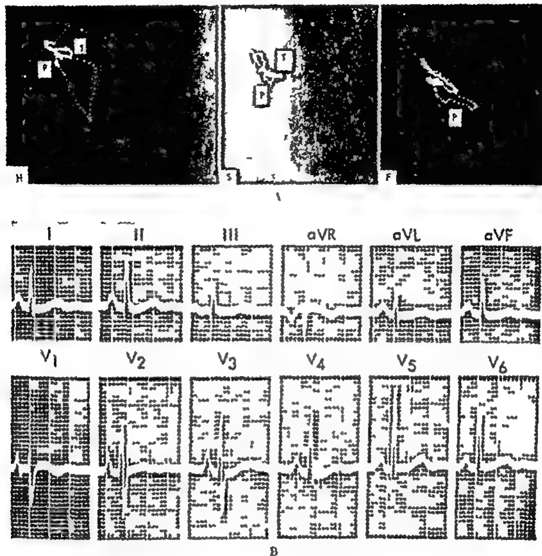


Fig 62 *A* Vectorcardiogram indicating right atrial enlargement in a case of pure tricuspid stenosis The P loop is directed mainly anteriorly and somewhat inferiorly and to the left
B Electrocardiogram in the same case (Courtesy of Dr A Grishman)

or by an abnormally long interval between peaks of a bifid P in any lead regardless of voltage Asynchronism of the two atria has been demonstrated by direct right and left atrial leads during operation [41] The left atrium contracts later than the right and accounts for the latter portion of the P wave When a bifid P occurs normally the first peak is essentially due to right and the second to left atrial activation The normal time difference between right and left atrial activity is 0 03 to 0 04 second and this is the normal interval between the peaks of a normal bifid P wave In cases of left atrial hypertrophy bifid P waves occur more frequently than in normal persons the second peak (left atrial activity) is delayed to more than 0 04 second and usually the interval between the peaks measures 0 06 second In pulmonary heart disease especially when there was distinct evidence of pulmonary hypertension there were changes indicative of right atrial hypertrophy but no increase in the intervals between peaks when bifid P waves were present In mitral stenosis evidence of left atrial hypertrophy was indicated by P wave changes with increasing frequency in relation to the severity of symptoms In one third of the cases there was evidence of right as well as left atrial hypertrophy particularly when there was evidence

of associated pulmonary hypertension In constrictive pericarditis there were P wave changes indicative of left atrial hypertrophy and occasionally of hypertrophy of both atria [9, 79] Tall pointed P waves were observed in the precordial leads in cases of isolated pulmonic stenosis or when this lesion was part of the tetralogy of Fallot or combined with other lesions [III, 79] In atrial septal defect the P changes were more suggestive of left atrial hypertrophy

VECTORCARDIOGRAM OF ATRIAL ENLARGEMENT

Instead of the normal narrow downward vertical P vector loop the vector loop in left atrial enlargement is directed anteriorly and to the left in its initial portion (Fig 51) whereas the larger terminal portion is directed posteriorly and somewhat inferiorly and leftward The loop is broader and triangular, and may be open with counterclockwise inscription in frontal and clockwise rotation in sagittal projections [8] In *right atrial enlargement* the P loop is directed anteriorly, very slightly to the left and little, if at all, downward (Fig 52) Occasionally it has a triangular appearance The loop is usually larger than normal or in left atrial enlargement, and is generally open The maximum vector is in the first portion of the loop, which is directed anteriorly In combined atrial hypertrophy there are large early anterior and large late posterior leftward forces [65a]

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Chapter 6

ETIOLOGY OF CHRONIC (CONGESTIVE) HEART FAILURE

Circulatory failure has been classified into the acute and chronic forms (Chapter 4) The acute form which includes shock syncope and sudden death, is discussed in Chapter 12 *The present chapter and the succeeding five* chapters are concerned with the chronic form of circulatory failure which is generally known as congestive heart failure

This chapter presents the factors or mechanisms which render the heart incapable of maintaining an adequate cardiac output, or of maintaining it without the aid of extra cardiac compensations The etiology of congestive heart failure will be discussed under the following headings (1) Fundamental Mechanism, (2) Precipitating Clinical Causes, (3) Underlying Causes The mechanism by which this cardiac disability leads secondarily to the clinical manifestations of congestive heart failure is discussed in subsequent chapters (8 and 9)

THE FUNDAMENTAL MECHANISM OF CARDIAC FAILURE

When cardiac failure occurs shortly after a toxic, *infectious disease such as diphtheria,* we assume that sufficient muscle tissue has been destroyed or its contractility so greatly impaired by bacterial toxins that the heart is unable to maintain the circulation It is incomprehensible, however, why cardiac failure *so often develops in a patient whose valvular,* hypertensive or arteriosclerotic heart disease has appeared entirely static and well compensated Frequently we suspect a recurrent or intercurrent infection, a progressive diminution in the coronary blood supply physical strain or some other so-called precipitating factor, but we *are at a loss to understand* exactly how this factor induced cardiac failure Investigations to determine the mechanism of cardiac failure have been conducted along three lines (1) The pathologic changes in the heart which has failed (2) The relationship of cardiac hypertrophy to cardiac failure (3) The chemical changes in the heart

THE PATHOLOGIC BASIS OF CARDIAC FAILURE

Extent of Anatomic Alterations in Heart with Failure

It has long been customary to attribute cardiac failure to anatomic changes in the heart, Yet it is a striking fact that the pathologist can rarely make a diagnosis of cardiac failure by examination of the heart alone As a rule the lesions of rheumatic, hypertensive coronary atherosclerotic, syphilitic and other forms of heart disease remain essentially the same in any one of the mentioned diseases whether or not the heart has failed Frequently there is no evidence to indicate that the old valvular or myocardial lesions have undergone any recent change which might account for the onset of failure There is often no close correlation between the extent of myocardial disease or the degree of *valvular disturbance and the occurrence of* cardiac failure Extreme mitral stenosis aortic stenosis or aortic insufficiency, or severe narrowing of the coronary arteries with myocardial fibrosis and necrosis is found at postmortem examination in persons who showed no clinical evidence of cardiac failure during life Conversely the myocardium of persons with longstanding heart failure may show too few lesions to serve as an adequate anatomic basis for the clinical picture

Sometimes, of course, as in cases of multiple coronary occlusions with extensive myocardial fibrosis and infarction or of diphtheritic myocarditis there is no question that the extent and severity of the visible anatomic changes in the heart may account for the

development of heart failure Furthermore on a statistical basis the hearts in cases of cardiac failure show more conspicuous dilatation and hypertrophy more severe degrees of valvular disturbance, greater coronary narrowing or more extensive myocardial disease than the hearts of persons with similar disease but without a clinical history of heart failure Nevertheless there are so many instances in which there is a great disparity between the extent of pathologic changes in the heart and the clinical evidence of failure that the anatomic alterations in the heart cannot be considered a satisfactory, universal explanation for the occurrence of cardiac failure

Conflicting Opinions as to the Significance of Microscopic Cardiac Lesions

The myocardial basis of cardiac failure was stressed particularly because of the microscopic investigations of Krehl[10] Romberg[12] and other members of the Leipzig school of pathology Krehl[10] studied eight hearts with valvular heart disease and found significant fresh and old macroscopic and microscopic lesions in the endocardium, pericardium, myocardium and vessels In cases of typhoid fever, scarlet fever and diphtheria, Romberg[4] observed inflammatory lesions in the myocardium which he believed accounted for the symptoms of heart failure and the occasional occurrence of sudden death In cases of idiopathic cardiac hypertrophy with symptoms of failure, Krehl[10] discovered inflammatory infiltrations, degenerative changes and extensive scarring He concluded that heart failure was the result of these myocardial changes and not of the hypertrophy as such

The concept that the pathologic changes in the heart accounted for the occurrence and onset of cardiac failure received its first major attack from the investigations of Aschoff and Tawara[2] These observers showed that while inflammatory changes were often present in the myocardium in cases of rheumatic cardiovalvular disease, in many other cases of this disease and in the majority of other cases of chronic cardiac failure significant inflammatory lesions were absent or the changes were too slight to explain the development of heart failure Certain so-called myocardial abnormalities, such as a disproportion of sarcoplasm to myofibrils, pigmentation of fibers perivascular round cells and degenerative nuclear changes were demonstrated to be either normal occurrences or artifacts Aschoff and Tawara[2] concluded that, except in diphtheria, heart failure in the majority of cases of cardiovalvular disease, nephritis atherosclerosis infectious diseases, chronic pulmonary disease syphilis tumors or trauma was due not to the extent of the anatomic myocardial lesions but to disturbances caused by increased functional demands on the heart

Individual Pathologic Cardiac Abnormalities in Heart Failure

The following pathologic abnormalities have been described as a possible anatomic substratum for cardiac failure Only brief comments are made as these changes are discussed in detail in the chapters on the individual etiologic diseases In evaluating the following changes it is important to note (a) whether they are merely evidences of myocardial disease or indicative of cardiac failure (b) whether their extent, severity or location can adequately account for the occurrence of cardiac failure and (c) whether the changes are the cause or the consequence of cardiac failure

1 **Inflammatory Lesions in the Myocardium** Rheumatic heart disease is the most important example of myocardial disease with predominant inflammatory lesions But although the rheumatic lesions are usually widespread throughout the heart (p 816), an essential feature is their localization in the interstitial tissue with relatively little involvement of the muscle parenchyma It is difficult to understand how the observed pathologic changes can be responsible for heart failure when the active muscle appears intact On the other hand since cardiac failure appears frequently when there is active rheumatic myocarditis with or without significant valvular disease it is probable that the failure is due to some as yet anatomically invisible toxic functional disturbance which accompanies the anatomic interstitial lesions and impairs myocardial function

Similarly, interstitial inflammatory lesions of the heart appear in a variety of infections or infectious diseases which are occasionally accompanied by heart failure, but the pathologic lesions rarely appear adequate to explain the failure

2 **Degenerative Parenchymal Lesions in the Myocardium** Predominant degenerative changes of the myocardial fibers are seen in a variety of toxic and infectious diseases in dis

eases of metabolism such as diabetes, in anemias and vascular disturbances Usually these changes are not associated with cardiac failure But even when cardiac failure develops the anatomic lesions rarely appear to be an adequate cause

Exceptions are seen in the instances of congestive heart failure associated with *myocardial necrobiosis* Diphtheria is the classic example of myocardial failure apparently due to extensive destruction of myocardial fibers (p 908) The interstitial inflammatory lesions seen in this disease are less important secondary changes which only appear if the disease lasts more than a week or two In typhoid fever there are occasionally acute degenerative myocardial changes similar to Zenker's degeneration in the rectus abdominis and other striated muscles but cardiac failure is rare Fiedler's or isolated myocarditis which is often complicated by heart failure reveals essentially interstitial changes but occasionally there is severe fatty degeneration, autolysis and even disappearance of large portions of the myocardial parenchyma Coronary atherosclerosis with occlusion is the most important cause of necrobiosis of heart muscle Occasionally extensive areas of heart muscle are destroyed and replaced by fibrous tissue, and in these instances there is a convincing anatomic basis for heart failure Very often however heart failure develops without good correlation with the extent of the pathologic abnormalities

Among *degenerative lesions of the myocardial parenchyma* are included cloudy swelling fatty degeneration vacuolar and hydropic degeneration, as well as necrobiosis The concept of the fatty heart (*adipositas cordis*) as a clinical pathologic entity responsible for cardiac failure, heart block or sudden death has generally been discarded except in rare cases (p 629) Anemia or ischemia of the heart muscle definitely results in fatty change which appears as a characteristic linear streaking known as tigering But when heart failure occurs in hearts showing tigering there is usually an associated severe anemia or an atherosclerotic or syphilitic coronary narrowing or occlusion which accounts for both the tigering and the failure

3 **Myocardial Fibrosis** The term chronic myocarditis was formerly applied to cases in which the heart revealed more or less extensive fibrosis of the myocardium This term should be discarded because the fibrosis is rarely due to the healing of *chronic inflammatory lesions* as the name implies As a rule the fibrosis results from ischemic necrosis of the myocardium due to (a) mechanical occlusion of a coronary artery as in atherosclerotic thrombosis, (b) severe narrowing of a coronary artery[13] or its ostium as in atherosclerosis or syphilis, or (c) relative coronary insufficiency when the blood supply does not keep pace with cardiac enlargement[13] as in malignant hypertension and calcific aortic stenosis Only occasionally is the fibrosis and replacement of myocardial tissue sufficient to account for heart failure

4 **Mechanical Defects of the Heart** The pathologic lesions thus far considered have been situated in the myocardium Often the essential or predominant lesions involve the valves or consist of congenital abnormalities of the septa or great vessels These valvular or other defects usually place a disproportionate physical strain on one or more of the chambers of the heart The importance of these defects is attested by the observations that the chamber primarily affected is the one which fails first, and that the type of heart failure i e the clinical picture is determined by the failure of the chamber in question Thus with stenosis of the aortic valve the early symptoms of failure are determined by decompensation of the left ventricle, while with pulmonary stenosis it is the right ventricle which fails

These and other observations indicate the importance of mechanical disturbances independent of myocardial disease, in the development of cardiac failure However such mechanical strain cannot account for the instances of heart failure in which there are no valvular or other mechanical defects Neither is it clear why failure occurs suddenly in hearts with old valvular defects which have not recently been altered or why failure may be absent in many cases with severe mechanical defects or present in cases where these are slight Finally it should be emphasized that the cardiovascular abnormalities which increase the mechanical strain on the heart are usually associated with some myocardial disease e g, coronary atherosclerosis with essential hypertension active rheumatic myocarditis with valvular defects and in

older age groups coronary disease with rheumatic valvular defects and syphilitic narrowing of the coronary ostia with syphilitic aortic insufficiency

In conclusion neither the character extent nor localization of the visible macroscopic or microscopic myocardial lesions accounts satisfactorily for the development of cardiac failure in more than a minority of the cases On the other hand pathologic study in most cases reveals some myocardial valvular or vascular abnormality which is the *underlying basis* of cardiac failure We have yet to bridge the gap between this myocardial disease which underlies heart failure and heart failure itself The visible anatomic abnormalities may be evidence only of some important deleterious but invisible changes in the function or structure of the contractile muscle tissue In recent years the gap between cardiac disease and cardiac failure has been related to the pathologic physiology of cardiac dilatation and hypertrophy and the fundamental but invisible alterations in the muscle itself have been sought in chemical studies of the myocardium (infra) and myocardial contraction

CAUSES OF FAILURE IN THE ENLARGED HEART

The maintenance of normal cardiac function is dependent primarily on the functional capacity of the myocardium and the load against which it works The cardiovascular diseases which eventually lead to congestive cardiac failure increase the load on the heart or depress its functional capacity or both In Chapter 4 we have seen that cardiac dilatation and hypertrophy are the chief mechanisms by which the heart compensates (i e maintains its normal function) when either the mechanical load is increased or its anatomico functional capacity reduced In Chapter 5 we have noted that cardiac enlargement (dilatation and hypertrophy) occurs so often with cardiovascular disturbances that it is the cardinal clinical sign of cardiac disease Numerous experimental clinical and pathologic observations indicate that cardiac enlargement is the response to cardiac disease and that cardiac failure is the end result of a variable period of increasing cardiac enlargement Thus it has become epigrammatic that congestive heart failure is the failure of the enlarged heart We will now consider the possible factors which cause the enlarged heart to fail

1 Compensatory Limitation of Cardiac Enlargement

In disease as in health there is a limit beyond which the heart is incapable of compensating for circulatory strain In health the load of exercise may demand the maximum functional capacity of the heart beyond which unpleasant symptoms compel the individual to desist In disease the heart may be required to work continuously at or near maximum capacity because of the abnormal load of irreversible cardiovascular disease This is accomplished by cardiac enlargement but at the expense of cardiac reserve Cardiac function of the enlarged heart may be adequate with the patient at rest but the lack of reserve prevents the increase in output which physical exertion demands Eventually progressive myocardial disease e g, due to coronary atherosclerosis impairs the efficiency of myocardial contraction or diminishes the amount of available muscular tissue Consequently cardiac compensation cannot be effected regardless of the degree of cardiac enlargement The compensatory effectiveness of cardiac dilatation may be occasionally limited by the relatively indistensible pericardium but more often by progressive impairment of the physiologic fitness of the heart muscle

In the heart lung preparation Starling[13] found that the heart died within eight to ten hours Gradually the heart dilated as its functional ability deteriorated until the indistensible pericardium was filled and further dilatation was impossible Thereafter further myocardial deterioration was evidenced by a fall in cardiac output and a rising venous pressure i e heart failure

Pathologic studies also suggest that heart failure often arises when cardiac enlargement reaches the limit of its compensatory capacity Karsner, Saphir and Todd[22] found that the thickness of myocardial fibers could increase only to a relatively fixed dimension and that with increasing hypertrophy more and more of the fibers attained that maximum thickness Postmortem observations also disclose that extremely heavy hearts are usually encountered only in subjects who had suffered from congestive heart failure While cardiac enlargement is often observed without failure *chronic* congestive failure is infre-

quently seen without pronounced cardiac enlargement These observations appear to indicate that congestive failure usually develops when progressive cardiac enlargement reaches the limit of its capacity to compensate the cardiovascular strain This compensatory limit varies greatly in different hearts depending in part on differences in the contractile power and efficiency of the available heart muscle In any case, as with skeletal muscle, there is an optimum beyond which further dilatation of the heart muscle is not accompanied by increased force of contraction

2 Mechanical Inefficiency of the Enlarged Heart

Certain observations indicate that dilatation and hypertrophy, which arise as compensatory mechanisms carry in themselves the germs of failure Starling and Visscher[59] found in the heart lung preparation and Moe and Visscher[43] in the completely isolated heart that when the heart began to weaken and dilate, its oxygen consumption increased in proportion to its degree of dilatation This observation has been confirmed on the heart as a whole by Hemingway and Fee[25] and by Peters and Visscher [illegible] and more recently on the isolated cat s heart by Lorber [39] Since the tiring dilating heart continues to perform the same or a diminished amount of useful work despite its increased oxygen consumption, its mechanical efficiency is reduced below normal [21, 17]

Studies of oxidative metabolism and cardiac efficiency by means of coronary sinus catheterization and the nitrous oxide method[6] indicated a distinct difference in oxygen consumption in enlarged hearts, depending on whether the patient studied was or was not in failure [8] In the presence of increased diastolic volume of the heart without failure the myocardial oxygen consumption (and energy liberation) per unit weight of heart muscle was elevated In the presence of heart failure with increased diastolic volume, the myocardial oxygen consumption per unit weight was normal despite large increases in initial myocardial fiber length These findings were interpreted to indicate that oxidative metabolism increases with elongation in the initial fiber only in the absence of heart failure, and that heart failure is accompanied by a defective conversion of oxidative energy into useful work

One of the suggested reasons for the mechanical inefficiency of the enlarged heart is the enhanced load against which it works during the course of ventricular ejection, whereas the normal heart works against a diminishing load even though there is a rising intraventricular pressure after opening of the aortic valve [11] The load against which the ventricle contracts is equal to the intraventricular pressure multiplied by its internal surface area In the normal sized ventricle, expelling a normal stroke volume of blood, the reduction in surface area is greater than the rise in intraventricular pressure from the diastolic to the systolic level, hence the load diminishes In the enlarged ventricle only a relatively small reduction in its radius and therefore in its surface area occurs with the same stroke output, the rise in pressure exceeds the reduction in area and the load increases Because of its larger surface area the enlarged heart compared to the normal, must use more energy against a greater load during rising systolic intraventricular pressure before ejection Thus during systole, both during the isometric phase and during ejection, the enlarged heart consumes more energy than the normal although the useful work, as indicated by stroke output, is the same

It appears from the above studies that the enlarged diseased heart liberates more and more energy in proportion to its degree of enlargement As the useful work of the enlarged compensated heart remains normal in terms of cardiac output or is diminished, less and less of the increased total liberated energy is converted into useful energy during progressive cardiac enlargement Thus in humans as in the experimental animal the larger the heart the less its mechanical efficiency Mechanical inefficiency in itself does not necessarily cause cardiac failure However, it partially neutralizes the effect of increased energy liberation by the enlarged heart and thereby limits its compensatory potential [illegible] According to another school of thought cardiac failure is not associated with a reduction in mechanical efficiency but with a decreased oxygen consumption for any given diastolic size and therefore an inability to release energy [54, 33]

In attempting to transfer these varied observations to human pathology one misses data which would indicate whether there are differences in oxidative metabolism and mechanical efficiency between the elongated myocardial fiber which is greatly hyper

trophied and that which is little hypertrophied and between the elongated fiber which is greatly diseased and that which is virtually normal Clinical pathologic evidence suggests that mechanical stretch (cardiac enlargement) beyond a certain point may perse eventually lead to cardiac fatigue and failure (as in arteriovenous fistula), but disease of the heart muscle may be the determining factor in the failure of the enlarged heart

3 Physicochemical Disadvantage of the Hypertrophied Heart

When the heart dilates as a result of cardiovascular disease its muscle fibers become elongated so that a greater surface is available for physicochemical change This is probably the mechanism by which it is enabled to perform the same amount of work as before the injury But as we have seen this is accomplished with a greater expenditure of energy and less efficiency By some process still unknown (possibly because of the greater oxygen consumption or of greater surface for chemical change) dilatation is followed by hypertrophy That is the muscle fibers become thickened as well as lengthened and the diminished efficiency of the dilated heart is partly offset by a greater amount of muscular tissue But now the thickened fibers of the hypertrophied heart offer greater difficulty to physicochemical exchange with their nutrient capillaries and tissue fluids than the thinner fibers of the normal heart

The studies of Hill [9] have shown that the *rate of diffusion of oxygen through tissues* varies inversely as the square of the distance that the oxygen must traverse Thus if the thickness of a muscle fiber is doubled it would take four times as long for oxygen saturation of the fiber as before hypertrophy occurred Harrison Ashman and Larsen[25] found that the mean fiber thickness was 16 2 micra for normal hearts 24 5 micra for the enlarged hearts of persons without congestive heart failure and 31 8 micra for the enlarged hearts which had failed These figures suggest that the fibers of the moderately hypertrophied heart are unable to obtain an optimal oxygen supply and are constantly in danger of anoxemia while the fibers of the extremely hypertrophied heart are constantly suffering from some degree of anoxemia This is particularly so in the central portions of the fibers which are furthest removed from the capillary twigs on either side

This disadvantage of the hypertrophied heart with respect to oxygenation becomes intensified in the presence of tachycardia such as accompanies physical exertion For any given cardiac output the oxygen requirement increases with an increase in cardiac rate [11] At the same time tachycardia encroaches on the diastolic period during which almost all of the oxygen diffusion occurs Persistent tachycardias *due to disturbances in impulse formation and the tachycardia associated with* fever and infection also exaggerate the impairment of oxygenation of the hypertrophied heart and may precipitate cardiac failure The disadvantage of the hypertrophied heart with respect to the diffusion of oxygen probably applies also to the diffusion of other substances necessary for its nutrition and its performance of work as well as to the elimination of waste products

4 Deficient Blood Supply of the Enlarged Heart

The deficiency in oxygen diffusion through the hypertrophied muscle fibers is not compensated by a corresponding increase in the number of coronary vessels By the use of Krogh s equation for the tension differences necessary to cause oxygen diffusion between two points Harrison[24] has estimated that the normal coronary flow is just about adequate to supply oxygen to the average-sized fiber of the moderately hypertrophied heart of a person at rest But the average-sized fiber (about 40 micra) of the extremely hypertrophied heart would require a *coronary blood flow two to* three times as great as normal to receive proper oxygenation

A similar conclusion may be arrived at mathematically by considering each muscle fiber as a cylinder whose surface exposed to tissue diffusion is represented by $2\pi RL$ but whose volume of muscle mass is represented by πR^2L where R is the radius of its cross section and L its length Using 16 micra as the diameter of the average normal muscle fiber its exposed surface is $16\pi L$ and its volume $64\pi L$ In the greatly hypertrophied heart the fiber diameter may average 32 micra its surface being $32\pi L$ and its volume $256\pi L$ Thus while its active physicochemical surface through which nourishment may enter has been doubled the mass of tissue to be nourished has been quadrupled

Anatomic studies fail to reveal an increase in coronary vessels which would be necessary

to compensate for the increased requirements of the hypertrophied heart Wearn[63] found an average of one capillary per muscle fiber in the normal heart During hypertrophy the muscle fibers enlarge but the capillaries do not multiply consequently the average number of capillaries per unit area in the hypertrophied heart is considerably lower than that in the normal heart[51] Experimentally also the Shipleys with Wearn[66] found that the capillary coronary supply did not increase with the development of cardiac hypertrophy in rabbits Gross and Spark[73] noted that there was roughly an inverse relationship between the size of the heart and the number of arterioles and small arteries per unit area In hearts weighing 200 to 300 gm there was an average of 3 14 arterioles whereas in hearts weighing 500 to 900 gm there was an average of 1 13 arterioles per low power field

Despite these anatomic findings, recent studies of the coronary blood flow with the aid of coronary sinus catheterization indicate not only that the coronary blood flow per 100 gm of left ventricular muscle is normal in the enlarged heart, but also that (in one case studied) the failing like the normal, heart responds to exercise with a rise in coronary flow However efficiency declined as the heart was unable to utilize fully the energy derived from either oxygen or glucose catabolism[38]

Summary Causes for Failure of the Enlarged Heart

Cardiac dilatation and hypertrophy start as compensatory processes which by their presence reveal the existence of cardiac disease Increasing cardiac dilatation and hypertrophy mark the roadway from cardiac disease to cardiac failure Cardiac enlargement (dilatation and hypertrophy) predisposes to cardiac failure because

(1) It encroaches on cardiac reserve which is limited by the ability of the muscle fibers to elongate and to become thicker When the limit is reached, the heart can no longer compensate for additional mechanical strain or myocardial damage

(2) The enlarged heart is less efficient mechanically than the normal heart because it consumes a greater quantity of oxygen although it performs the same or a lesser amount of useful work

(3) The thickened fibers do not permit as rapid a diffusion of oxygen, nutriments and metabolites as the normal fibers In extremely hypertrophied fibers there is constant anoxemia even when a person is at rest In moderately hypertrophied fibers anoxia occurs readily during exertion or with any arrhythmia or disease which increases the heart rate and reduces the diastolic period of recovery

(4) The blood supply to the fibers of the hypertrophied heart may not increase pari passu with its enlargement Thus despite the greater requirement of oxygen because of the greater muscle mass to be nourished and the greater amount of total work, oxygen diffusion is impaired Thus there is a relative coronary insufficiency even when the coronary vessels are normal This deficiency becomes greatly intensified in the course of years if the coronary vessels become narrowed by atherosclerosis

THE CHEMICAL BASIS OF CARDIAC FAILURE

Ultimately the cause of cardiac failure must be sought in disturbances of the chemical processes which provide the energy for transformation into mechanical work Our still primitive knowledge of the chemical basis of heart failure comes chiefly from three types of investigation (1) Formerly, most studies were concerned with determinations of the chemical composition of the blood during life or of heart muscle obtained at autopsy from subjects with heart failure and from subjects with normal hearts Or studies were made of the chemical composition of blood or heart muscle in experimental animals after anoxemia or coronary occlusion since these were regarded as major factors in the production of heart failure (2) More recently the development of the technique of catheterization of the coronary sinus in conjunction with the use of the nitrous oxide method for determining blood flow has yielded important information as to oxygen consumption and the utilization of various foodstuffs in health and disease, including heart failure[8] (3) Increasing knowledge regarding muscular contraction and techniques for the in vitro study of actinomyosin, the muscle protein complex which is the basic contractile material gives promise of important progress in the direct approach to the understanding of the myocardial disturbances responsible for heart failure

Myocardial Metabolism and Cardiac Contraction[67 43 60 61 44 7]

Our knowledge of the mechanism of myocardial contraction is based chiefly on our

knowledge of contraction of skeletal muscle and the assumption that they are essentially similar Nevertheless it should be mentioned that cardiac muscle differs from skeletal muscle in several anatomic chemical and physiologic aspects, and most important in its capacity for continuous rhythmic contraction for many decades Cardiac work is largely dependent on aerobic metabolism in contrast with the activity of skeletal muscle in which metabolism is dominated by an aerobic, glycolytic systems This dependence of the heart on oxygen and its intense oxygen utilization is indicated by the very low oxygen content of its coronary sinus (venous) blood which averages 5 to 7 volumes per cent in contrast with about 14 volumes per cent for mixed venous blood Heart muscle is well adapted for its oxygen needs by its unusually rich blood supply each fiber being adjacent to one or more capillaries and its blood flow which forms 5 per cent of total blood flow by the absence of a membrane separating myofibril from capillary such as exists in skeletal muscle and by its much greater supply of oxidative enzymes (cytochromes and succinic dehydrogenase) At the same time heart muscle is more susceptible than skeletal muscle to oxygen lack because of the greater dependence of its metabolism on oxygen

Cardiac contraction involves an adequate supply of the raw materials (substrates oxygen enzymes hormones) and a sequence of complicated processes from the initiation of the activation stimulus and its transmission, to depolarization of the myocardial cell and the various chemical processes concerned with the generation and utilization of energy and their translation into contraction and relaxation of the muscle fibers It is probable that cardiac failure may result from disturbances in individual factors or in several steps in the process Investigations are designed, among other purposes to determine whether specific clinical types of heart failure can be correlated with disturbances in different stages of the contraction process and whether therapeutic measures can be utilized in more direct application to the deficiency in the contractile process which is responsible for the heart failure

The essential elements in cardiac metabolism and cardiac contraction are (1) the food stuffs or fuel which act as oxidizable substrates and serve as the ultimate source of energy, (2) actin, myosin and their conjugate actomyosin which is the contractile protein of muscle, (3) adenosine triphosphate which provides high-energy phosphate bonds ($\sim P$) to energize contraction of actomyosin (4) potassium and other ions (5) phosphocreatine (6) various enzymes, hormones and muscle proteins

Production of Energy for Contraction The *major fuel or source of energy is glycogen* which is derived from blood glucose Blood lactate and pyruvate may also be used directly, the extraction of glucose, lactate and pyruvate by the heart being proportional to the concentration of these substances in the coronary artery blood With strenuous exercise, lactate and pyruvate utilization may account for the major oxygen consumption while in starvation and acidosis the ketone bodies are used for oxidation while carbohydrate is spared Fatty acids and amino acids may also serve for energy production

After phosphorylation and intermediate steps in metabolism, glucose is broken down to pyruvate molecules, while at the same time lactate is oxidized to pyruvate with the aid of a coenzyme derived from nicotinic acid In the course of normal aerobic catabolism pyruvate molecules are eventually oxidized to carbon dioxide and water with the release of most of the energy required for cardiac work Under anaerobic conditions the pyruvate is reduced to lactate in the course of which only one tenth of the glucose energy is released which is inadequate for cardiac work Furthermore the lactic acid accumulates as an end product in heart muscle and blood

During aerobic metabolism the pyruvate is broken down to high-energy two-carbon active acetate These two-carbon molecules are combined enzymatically with a four carbon molecule oxalacetic acid to yield citric acid Thereafter through the Krebs tricarboxylic or citric acid cycle,[35] with the aid of vitamins and coenzymes two-carbon fragments and their associated hydrogen atoms are removed in steps by oxidative reactions

The released hydrogen does not combine directly with oxygen but is passed on to a series of enzymes (flavoproteins and cytochromes) which act as hydrogen carriers With each step in this series of enzymatic dehydrogenations the energy derived from carbohydrate substrate, now accompanying the detached hydrogen atoms, is released to

each enzyme hydrogen carrier and transferred to phosphate, forming high energy phosphate bond (indicated ~P) The high energy phosphate bond is stored in the muscle fiber after combination with special acceptors notably nucleotide phosphate and creatine The nucleotide adenylic acid combines with one ~P group to form *adenosine diphosphate* (ADP) or with two ~P groups to form *adenosine triphosphate* (ATP) The synthesis of ATP is localized in the mitrochondria (sarcosomes) of the heart muscle cells [31] The combination of creatine with one high-energy phosphate group forms phosphocreatine Phosphocreatine acts as a storage form of ~P and yields its ~P after myocardial contraction to adenosine diphosphate and restores high energy adenosine triphosphate These high-energy phosphate carriers yield their ~P as required for myocardial contraction and relaxation

Muscle Proteins and Myocardial Contraction

Myosin is an elongated fibrous protein conjugate, with a molecular weight of 850 000 usually combined with magnesium, but with a marked capacity to bind other ions such as potassium and calcium The myosin molecule has recently been shown to be composed of four thin, elongated and relatively light (L) meromyosin molecules, strung together lengthwise in series and two shorter and heavier (H) meromyosin molecules lying beside the end L-meromyosin molecules Muscular contraction or shortening appears to be due to the folding of the thin and elongated L-meromyosins, which are sensitive to small changes in ionic concentration Potassium ions form a positively charged atmosphere which causes the ends of the myosin fibril to repel each other and therefore the fiber to remain straight and extended The H molecules of the myosin complex serve as an anchor have a strong affinity for magnesium and adenosine triphosphate and link the myosin to actin The ATPase activity of myosin is due to the H meromyosin

Actin exists as a "globular' protein colloid G actin, with a molecular weight of 57,000 and as a polymerized "fibrous' protein F actin Most of the calcium in the muscle is probably bound to actin G actin is unstable and in the presence of low salt concentrations (e g, 0 1 M KCl), myosin causes its rapid polymerization to threads of F actin Magnesium and ATP appear to be essential for this actin G F transformation The ATP is dephosphorylated to ADP in the course of this polymerization, yielding a high energy phosphate bond to the actin molecules The polymerization of actin is apparently an essential chemical reaction in the contraction process, and occurs prior to or during the rise of tension and coincidentally with the initial heat production The contraction of 1 gm of muscle is accompanied by a breakdown (dephosphorylation) of 0 5 μM of adenosine triphosphate

Myocardial Contraction [44] ■ [60] [19] ■ The following abbreviated summary of the process of muscular contraction has many points of uncertainty due to gaps in our knowledge but represents the essential features of the hypothesis as formulated by Szent Gyorgy and his associates

Prior to systole, F actin and myosin exist in muscle dissociated from each other While attracted by colloidal forces, they are repelled and kept apart by the potassium ions present in muscle cells The cell membrane is polarized The linked meromysin molecules are straight i e, unfolded

The excitatory impulse initiated at the sinoauricular node depolarizes the cell membrane and causes it to become permeable to ions, notably potassium There is an egress of potassium ions with a reduction in the potassium gradient The reduction in muscle cell potassium concentration now permits the union of actin and myosin to form very long molecules of viscous, doubly refractile strings of actomyosin This precipitation of myosin by actin is an example of the method by which a charged protein is discharged

Following *membrane depolarization* and *reduction in cellular potassium* the ATP becomes adsorbed onto myosin and the combined actomyosin is actually an actomyosin ATP complex The presence and concentration of potassium magnesium calcium and perhaps other ions and the pH, are important in the regulation of this reaction and subsequent contraction The linkage of ATP to actomyosin gives the actomyosin tensile strength and somehow makes the meromyosin joints more pliable permitting folding of the muscle protein

Either the actomyosin, as a magnesium complex, or some other substance in muscle acts as an ATP phosphatase so that a *high-energy phosphate bond is split off the ATP* and

supplies the actomyosin fiber with energy for contraction Adenosine diphosphate is the residual of the split ATP molecule[33] About one tenth of the ATP may be converted into a new component, nucleotide II[34]

The charged actomyosin ATP or ADP complex first contracts isometrically increasing the tension of the elastic portion of the muscle fiber, then *shortens maximally* as the elongated molecules fold on each other The actomyosin complex becomes discharged with shortening its energy being partly converted into work performed by contraction, the remainder of its energy being dissipated as heat

Relaxation includes the following processes

1 Potassium reenters the cell and the cell membrane becomes polarized

2 ATP is regenerated from ADP and its high-energy phosphate bone is restored chiefly by the labile ~P obtained in the enzymatic oxidations of glucose, glycogen lactic and pyruvic acids This depends on a continuous oxygen supply In the absence of such a supply or when it is temporarily inadequate as during severe physical exertion and until adequate labile ~P becomes available the high-energy phosphate bond required to regenerate ATP from ADP is supplied by phosphocreatine which is the most important storage form of high-energy phosphate The creatine that is left regenerates phosphocreatine by accepting high-energy phosphate bonds as a result of carbohydrate oxidations

3 Actomyosin is separated from ATP and actin is dissociated from myosin because of the increase in potassium concentration and restoration of ionic equilibrium Perhaps actin F is transformed back to actin G A soluble muscle protein *(the Marsh factor)* in the presence of adenosine triphosphate may be important in causing relaxation[41 2]

4 The folded shortened actomyosin threads, having been discharged now become recharged unfold and become straightened Elongation may also result from its elastic property

Cardiac Muscle Metabolism and Heart Failure

From the physiologist's viewpoint cardiac fatigue or cardiac failure is characterized by an inadequacy of cardiac capacity to perform work relative to the load imposed upon the heart Or more practically the blood supply provided by the contracting heart is inadequate for the demands of the tissues throughout their ordinary range of activities It would be of the utmost value to know, at least as an early step toward progress what is the chemical physiologic basis of heart fatigue and failure in terms of the various steps in the metabolism and energetics of cardiac contraction and restoration

From this viewpoint cardiac failure may be related to (1) an inadequacy of the raw materials forming the substrate needed to produce high-energy bond phosphate or a deficiency in the generation of such (2) an inadequacy of muscle or muscle proteins required for contraction or (3) an impairment in the utilization of this energy for muscular contraction and its transformation to useful work

1 An inadequacy of raw materials to generate energy is rarely responsible for clinical heart failure except possibly in unusual cases of prolonged dietary deficiency Lack of accessory materials notably enzymes and coenzymes occasionally is associated with heart failure This probably applies to beriberi heart disease in which thiamine inadequacy is responsible for deficiency of the coenzyme cocarboxylase which is concerned in the oxidation of pyruvate to active acetate (acetyl coenzyme A) Consequently there is an interruption in the oxidative processes which produce the energy needed for myocardial contraction Lack of oxygen is the most obvious factor which may be responsible for heart failure by reducing or eliminating the aerobic metabolic processes which generate most of the needed energy Wohl et al[33] found a significantly lower concentration of thiamine and cocarboxylase in the hearts of patients who died of congestive heart failure (not due to beriberi) than in the hearts of those who died of other causes

Actually the relation of oxygen lack to clinical heart failure is not clear cut The two commonest diseases associated with heart failure are hypertension and coronary atherosclerosis In the former oxygen lack plays a part only insofar as the associated cardiac enlargement imposes a theoretical disadvantage to oxygen diffusion in the myocardial fiber but as we have seen experimental evidence indicates that there is no deficiency in energy production in the enlarged heart In coronary heart disease oxygen lack is more distinctly associated with pain than with heart failure Severe anemia is the most direct example of oxygen deficiency as a factor in

heart failure, but as a rule anemia induces heart failure only in the presence of intrinsic heart disease. Hyperthyroidism, too, has been regarded as an indirect cause of oxygen lack, i.e., relative to the high level of myocardial as well as general tissue metabolism. Hyperthyroidism rarely, if ever, causes heart failure unless there is associated cardiac disease. Thus it is difficult to correlate the vast majority of cases of heart failure with any impairment of energy production due to lack of the common foodstuff substrates of enzymes and coenzymes or even of oxygen.

Cases of heart failure due to anemia, thiamine deficiency and hyperthyroidism have in common the incomplete oxidation of carbohydrate with consequent accumulation of lactic and pyruvic acids which cause peripheral vasodilatation. These cases also have in common an absolute high cardiac output despite heart failure, albeit the high output is insufficient for cardiac needs. High output failure may thus be regarded as the form of heart failure due to impairment of energy production. However, it is improbable that the latter is the sole or even major cause of the heart failure because (a) there is almost always associated cardiac disease of other etiology, (b) the high cardiac output and therefore the increased work of the heart result not from the effects of incomplete oxygenation and accumulation of acid metabolites in the myocardium, but from these effects on peripheral tissues and (c) the same type of high output failure is observed in the purely mechanical arteriovenous fistula in which there is no question of impaired myocardial energy production. The vasodilatation in anemia, beriberi and hyperthyroidism may be regarded as producing the equivalent of an arteriovenous shunt, and the heart failure, as in traumatic arteriovenous fistula, may result from the effects of the increased load on the heart.

2. An inadequacy of contractile substance, namely actomyosin or its precursor proteins, can rarely be considered as the cause of heart failure. Such a causative relationship may apply to occasional instances of diphtheritic myocarditis with extensive muscle degeneration and necrosis, and perhaps to some cases of multiple coronary occlusions with extensive myocardial necrosis and replacement fibrosis. However, extracts of homogenized cardiac muscle from dogs with experimental chronic heart failure showed a decreased concentration and viscosity of actomyosin and a decreased viscosity response on addition of ATP in comparison with similar muscle extracts from normal dogs.[4] These and related studies suggested that in the failing myocardium actomyosin is found in a partially dissociated (depolymerized) state.

Thus heart failure may be due to a physicochemical change in the character of actomyosin rather than in an inadequate amount of the protein. The physical or molecular structure of myosin or actomyosin is probably of great importance in the performance of mechanical work during contraction of the myofibril. In experimental heart failure in the dog there were noted marked changes in the physicochemical properties of cardiac myosin which were consistent with a considerable increase in molecular weight.[48, 47a] The effect of purely mechanical stresses in inducing cardiac failure also suggests that physical changes in the structure of the contracting muscle protein may be important.

3. A defect in the utilization of energy, either because of impairment in the transfer of high-energy phosphate bonds to actomyosin or an impairment in the conversion of this energy to useful work, appears to be the most likely physical-chemical basis of the common forms of heart failure associated with cardiac enlargement, such as hypertension and rheumatic cardiovalvular disease. This is based on the failure to find adequate evidence for a deficiency in energy production either in studies with the heart lung preparation or in studies of coronary sinus catheterization in humans which showed that oxygen extraction and substrate utilization were essentially normal in the enlarged and failing heart. Since the cardiac output was diminished when oxygen utilization was normal, it appeared that there was impairment not in energy production but in conversion of this energy to useful work. The possible relation of disturbances in cationic concentrations, particularly intracellular potassium and sodium, to this impairment in the transfer and utilization of energy is discussed on page 136. A defect in the utilization of energy to produce useful work may be due to changes in the physicochemical structure of actomyosin as suggested above, or to disturbances in enzyme content or structure, e.g., the relative content and speed of interconversion of the monomeric and dimeric forms of phosphorylase

Disturbances of the Glycogen Cycle The concentration of glycogen in the myocardium is a constant with normal activity and even with hypoglycemia. Myocardial glycogen is depleted only with complete anoxia and with epinephrine. On the other hand it may actually rise with starvation and with diabetic ketosis presumably because lipids and ketone bodies are utilized and carbohydrates spared[27, 8]. There is evidence that relative anoxemia present in the hypertrophied and failing heart interferes with the aerobic oxygenation of lactic and pyruvic acid and the consequent energy formation required for muscular contraction. Studies of experimental anoxemia[20] and coronary occlusion[30] revealed a reduction of cardiac glycogen especially in infarcted areas, and an accumulation of lactic acid in blood and muscle. Herrmann and Decherd[7] found a similar loss of glycogen in the infarcted areas of human hearts. Other observers have stressed the finding of increased lactic acid in the blood of patients with congestive heart failure[42] particularly because of experimental evidence that the mammalian heart is much more readily exhausted by the accumulation of lactic acid than is skeletal muscle[50]. However it is more probable that increased blood lactic acid is the result and not the cause of cardiac failure. A rise in the pyruvic acid concentration of the blood has been found in patients with congestive heart failure[65]; it probably has the same significance as the rise in lactic acid.

Disturbances of Phosphocreatine Metabolism The fact that phosphocreatine is an *immediate* source of energy for muscular contraction and that it is reduced in skeletal muscle in certain forms of myasthenia and muscular dystrophies suggests that cardiac fatigue and failure may be due to a loss of myocardial phosphocreatine or to a disturbance in its metabolism. Since phosphocreatine is a very labile compound it cannot be determined directly at autopsy; but creatine concentration was taken as a measure of its quantity during life. A higher creatine concentration has been found in the left than in the right ventricle and this has been correlated with the greater strength of contraction of the former[55]. However the difference in creatine concentration may be insignificant if allowance is made for the greater amount of extracellular water, fat and connective tissue in the right ventricle.

With slight increments in heart weight the creatine concentration was found to increase but with progressive cardiac hypertrophy there was a corresponding reduction in creatine[47]. In hearts of persons dying of congestive heart failure a substantial diminution in the cardiac creatine concentration has been uniformly observed[32, 40]. In cases of cor pulmonale the creatine concentration has been reported to be reduced in the right ventricle but not in the left[40]. The observed reductions in cardiac creatine in heart failure, like those of glycogen, have been related to deficient oxygenation, for similar low values for creatine in heart muscle have been found following asphyxia and myocardial infarction due to coronary artery occlusion[3]. However there is considerable doubt whether determinations of total creatine post mortem can be used as a measure of phosphocreatine during life. For there is experimental evidence based on simultaneous determination of myocardial creatine and phosphocreatine that there is a poor correlation between total creatine and phosphocreatine concentrations[47].

Phosphorus Metabolism Phosphorus concentrations in cardiac muscle have also been found to be reduced in congestive heart failure[6]. The total phosphorus in the heart consists of an acid soluble fraction (soluble in 5 per cent trichloracetic acid) and an acid insoluble fraction. The acid soluble fraction comprises the so-called activity substances including phosphocreatine, hexosephosphate, adenosine triphosphoric acids, all important in muscular contraction. It is this acid soluble phosphorus fraction which accounts chiefly or entirely for the reduction in cardiac phosphorus in heart failure[16].

The acid insoluble phosphorus fraction consists of lipids or phosphatids. Various observers have noted a reduction in myocardial lipids in the fatigued experimental heart and in the hearts of persons dying of heart failure. However there is some doubt as to whether the reduction in cardiac lipids is statistically significant. Theoretic importance has been attached to the cardiac lipids because of their higher concentration in cardiac than in skeletal muscle and because of their active role in surface phenomena.

Adenosine Triphosphoric Acid A reduction in adenosine triphosphoric acid in the hearts of patients dying of congestive heart failure

has been revealed indirectly by determination of the nitrogen of the purines convertible to oxypurines.[40] The fact that the reduction of potassium and phosphorus exceeds the reduction in heart muscle creatine suggests also that this difference is due to a concomitant loss of adenosine triphosphoric acid, which like phosphocreatine contains phosphorus and is combined with potassium. The fact that dephosphorylation of ATP takes place in the heart after its removal from the body indicates that the determination of easily hydrolyzable phosphate, as often done to measure ATP, would lead to underestimation of this nucleotide.[34]

Potassium and Sodium. The important role of potassium in the contraction of heart muscle has been discussed. Recent evidence suggests that disturbances in intracellular as well as extracellular potassium may be of importance in the impairment of cardiac contraction associated with heart failure. Extracellular sodium is a key factor in producing the *clinical features* of congestive heart failure (Chapter 7). But intracellular sodium, like intracellular potassium, may be concerned with the fundamental chemical disturbances which are the primary basis for inefficient cardiac contraction and cardiac failure. Although the employment of radioisotopes of potassium and sodium has helped in the estimation of these intracellular ions, highly satisfactory methods for this purpose are not available. The difficulty of determining intracellular potassium and sodium is enhanced in the presence of congestive heart failure.

Studies of tissues at autopsy indicated that the potassium concentration of heart muscle was diminished. Recent studies of this type confirmed the reduction in myocardial potassium concentration and indicated that this reduction was not due to heart muscle edema, as the total water content of normal hearts and those from patients dying of congestive heart failure was the same.[1, 2] Furthermore it was found that the reduction in potassium concentration in dried heart tissue was accompanied by a similar increase in sodium concentration in hearts that had failed and that the sum of potassium and sodium remained the same in normal and failing hearts. There was indirect evidence also that the beneficial effect of digitalis was related to its normalizing influence on myocardial electrolyte balance.

The concentrations of potassium and sodium appear to have an important influence on the phosphorylation of AMP (adenosine monophosphate) and ADP (adenosine diphosphate) to ATP and on the phosphorylation of creatine to phosphocreatine, the steps by which energy produced in cardiac metabolism is transferred for later utilization in contraction. Phosphorylation of creatine is stimulated by potassium and is optimum at potassium ion concentrations of about 50 to 200 mEq./liter,[10] while the average body intracellular concentration of potassium is 112 mEq./liter.[15] Significant reductions in myocardial potassium concentration, as suggested by the above-mentioned studies, might seriously impair this important process of energy transfer. Conversely, increased intracellular sodium ion concentration interferes with the transfer of high energy phosphate to creatine and the conversion of AMP and ADP to ATP with a similar transfer of energy.[8] Sodium ion concentrations of 35 mEq./liter or more have such an inhibitory effect. Since the average intracellular sodium concentration for the body as a whole is about 37 mEq./liter,[15] a relatively slight increase in myocardial cellular sodium would significantly interfere with energy transfer and myocardial contraction, assuming that intracellular myocardial sodium did not vary much from the body average intracellular sodium. There is also evidence that the force of myocardial contraction is dependent on the *total quantity* of sodium and potassium within the muscle fiber.[60, 61] Present-day theory of myocardial contraction assumes that the egress of potassium out of the myocardial cell (and the inflow of sodium ion) is an essential feature of depolarization as well as of the formation of the actomyosin ATP complex necessary for cardiac contraction. If heart failure is associated with low intracellular potassium and elevated intracellular myocardial sodium, the disturbance in ionic intracellular-extracellular gradient might interfere with these processes of depolarization and contraction. They would also suggest some disturbance in the intracellular mechanisms controlling sodium potassium concentrations in congestive heart failure.

In summary, chemical studies of hearts of individuals who had died of heart failure indicate significant changes in those substances which are now considered of fundamental

importance in muscular contraction There is indirect evidence of a loss of myocardial glycogen and direct evidence of a reduction in myocardial creatine total and acid soluble phosphorus compounds potassium and possibly lipid and an increase in intracellular sodium The significance of these findings is somewhat uncertain in view of the questionable reliability or indirectness of the methods employed and because of possible doubt as to the applicability of studies of myocardial tissues post mortem and of in vitro studies to living myocardium

PRECIPITATING CLINICAL CAUSES OF CONGESTIVE HEART FAILURE

While the fundamental cause for the onset of congestive heart failure is still obscure a clinical precipitating factor can often be determined Of 100 cases of cardiac failure studied by Sodeman and Burch[47] failure was precipitated by some demonstrable factor in 53 while in 47 it developed gradually without apparent cause

1 Infections

Myocardial failure in the cardiac patient is very often precipitated by (a) infections which directly increase the myocardial disease or (b) intercurrent infections which incidentally impair cardiac function or otherwise induce heart failure

(a) Rheumatic fever is the prime example of a disease related to infection which may cause cardiac failure by direct action on the heart Rheumatic fever is the commonest cause of cardiac failure between the ages of 10 and 40 The onset of heart failure after a more or less prolonged period of inactive rheumatic heart disease has been frequently attributed to recurrent rheumatic activity The studies of Rothschild Kugel and Gross[52] on 161 rheumatic hearts of persons who had died of congestive heart failure showed that up to the age of 20 95 to 100 per cent of the hearts revealed signs of active rheumatic carditis between the ages of 20 and 40 about 75 per cent disclosed such signs and even after the age of 40 cardiac failure was associated with active rheumatic myocardial lesions in one fourth of the cases Biopsies of left atrial appendages from patients subjected to mitral commissurotomy for severe mitral stenosis revealed a high incidence of lesions regarded as signifying active rheumatic inflammation

Nevertheless in adult life certain other factors seem more important than rheumatic activity in the precipitation of heart failure in rheumatic hearts The pathologic and biopsy studies indicating the presence of Aschoff bodies do not denote a corresponding, clinically significant rheumatic activity

(b) Intercurrent infections especially those of the respiratory tract very often lead to the development of congestive heart failure but usually only in patients with preexistent chronic cardiac disease It should also be emphasized that upper respiratory infections predispose to attacks of rheumatic fever and thus indirectly may cause cardiac failure Subacute bacterial endocarditis is not infrequently complicated by congestive cardiac failure either because of increased valvular deformity or destruction and myocardial damage

The mechanisms by which infections especially respiratory infections may induce cardiac failure are (1) Increased work of the heart due to fever and tachycardia (2) Toxic effect on the myocardium which is not demonstrable anatomically (3) Diminution of the diastolic period of recovery because of tachycardia This factor is particularly harmful in the hypertrophied heart (4) Cough in respiratory infections may represent intense muscular exertion and a severe strain on the heart in persons with cardiac disease (5) Infections may be associated with impairment of renal excretion of sodium

2 Inadequate Coronary Blood Flow (p 129)

We have already discussed the theoretical importance of a diminished coronary blood flow in causing cardiac failure In emphasizing that it is usually the large heart which fails we considered the relatively inadequate coronary blood flow and impaired diffusion of oxygen to the hypertrophied fibers and the effect of the resulting anoxemia on cardiac metabolism We often observe the cardiac patient who remains well compensated until coronary artery disease develops in middle or old age In rheumatic cardiovalvular disease in hypertension and in luetic aortic insufficiency cardiac failure often develops only when coronary atherosclerosis (narrowing or occlusion) adds its baneful influence to that of valvular or cardiovascular disease In these cases the cardiac hypertrophy is an effective compensatory mechanism until coronary insufficiency interferes with the increased needs for oxygen In addition acute coronary oc

clusion, by causing extensive damage to heart muscle, may precipitate failure in a heart which was not previously enlarged

3 Changes in Rate and Rhythm

Paroxysmal tachycardia, in which the heart rate is often 200 per minute or more occasionally precipitates congestive heart failure if the attack is prolonged As a rule this occurs in patients with underlying organic heart disease, but occasionally it may occur in the presence of a normal heart In infants and children paroxysmal tachycardia and/or congenital heart disease are the commonest causes of congestive heart failure Rapid ventricular rates (over 100) with atrial fibrillation or atrial flutter often lead to failure of the diseased heart or at least are associated with the onset of cardiac failure Tachycardia interferes with myocardial contraction not only by preventing proper oxygenation in an hypertrophied heart but also when the rate exceeds 180 per minute by seriously reducing the diastolic recovery period and preventing adequate cardiac filling In patients with tight mitral stenosis any factor which induces tachycardia may precipitate acute left atrial failure (pulmonary edema)

4 Excessive sodium intake may precipitate acute left heart failure [redacted] g after several successive meals of high sodium content

5 Discontinuation of digitalis may induce decompensation after cardiac failure had been controlled

6 Pregnancy and Childbirth

Heart failure sometimes develops in the course of childbirth or pregnancy in patients with previous heart disease (Chapter 47) Acute pulmonary edema is occasionally observed in patients with mitral stenosis and pulmonary congestion It is now recognized that in persons with well compensated heart disease, heart failure during pregnancy and childbirth occurs with extreme infrequency On the other hand in patients with previous attacks of heart failure or in those with limited cardiac reserve congestive heart failure occurs commonly

7 Hemorrhage and Anemia

Anemia [redacted] not infrequently associated with cardiac enlargement and sometimes with congestive heart failure In persons with chronic cardiac disease heart failure may be induced by progressive anemia or acute loss of blood I have seen heart failure precipitated in two patients with hypertensive and [redacted]therosclerotic heart disease and in one with rheumatic cardiovalvular disease immediately after an acute hemorrhage due to a peptic gastric or duodenal ulcer I have also seen cardiac failure develop in a patient with hypertensive cardiovascular disease with a hemoglobin of 17 per cent due to a chronic bleeding hemorrhoid These precipitating factors of cardiac failure are important to recognize because they can sometimes be prevented Treatment may beneficially affect the manifestations not only of the anemia but of the heart failure

8 Pulmonary Embolism

I have repeatedly observed cardiac failure induced by pulmonary embolism, especially in patients with rheumatic heart disease In some instances persistence or recurrence of heart failure is related to repeated embolization In many of these cases the precipitation of heart failure [redacted] erroneously attributed to bronchopneumonia

9 Transfusions and Sodium Containing Infusions

These not infrequently precipitate heart failure in patients with organic heart disease and in elderly patients without overt evidence of previous heart disease They may also induce heart failure in patients with acute glomerulonephritis toxemia of pregnancy or toxic nephrosis with severe oliguria or anuria

10 Physical and Emotional Strains

Acute overexertion occasionally initiates congestive heart failure and then only in persons with diseased hearts It [redacted] uncertain to what extent *prolonged* overexertion contributes to the occurrence of heart failure Sodeman and Burch[87] and others list exercise as the most common precipitating factor of cardiac failure, but it is not clear what degree or form of exercise [redacted] responsible or what is the exact relationship to failure Insurance statistics which indicate that long continued and strenuous labor adversely affects the heart fail to account for many associated factors such as differences in constitution, heredity and social and economic status

Occasionally heart failure appears to be precipitated by experiences which involve considerable physical and emotional strain For example pulmonary edema or other evidences of congestive heart failure may appear after surgical operations coitus or prolonged worry and anxiety Surgical operations may lead to coronary insufficiency or myocardial infarction with subsequent heart failure as [redacted]

result of a fall in blood pressure and shock The tachycardia and elevation of blood pressure may be the factors responsible for heart failure after coitus In both of these as well as in various states of fear and anger the cardiac output and work of the heart may be increased

11 Environmental Heat and Humidity

A rapid elevation in atmospheric temperature and humidity may precipitate acute left ventricular failure in subjects with cardiac disease and diminished cardiac reserve Impaired dissipation of heat causes marked vasodilatation of superficial vessels with increase in cardiac rate and speed of the circulation thereby augmenting the venous return and load on the heart[5]

SIGNIFICANCE OF THE PRECIPITATING CAUSES OF CONGESTIVE CARDIAC FAILURE

It is important to recognize the *precipitating* causes of heart failure for we can more readily avoid or eliminate these causes than we can other factors in the development of heart failure For the present the avoidance of these precipitating factors offers the most direct and the most promising approach to the prevention or postponement of heart failure The fundamental basis of heart failure is still obscure while the underlying causes are usually not susceptible either of prevention or treatment

Recognition of the precipitating cause of cardiac failure is important in the prognosis as well as treatment of this condition Sodeman and Burch[57] found that of 47 cases of cardiac failure without detectable precipitating cause 46 were unable to restore cardiac compensation despite treatment On the other hand of 54 cases with a demonstrable precipitating factor compensation was rapidly established in 40 Thus the outlook in a given case of heart failure is much better when a definite precipitating factor is present

UNDERLYING CAUSES OF CONGESTIVE HEART FAILURE

For practical as well as theoretical reasons we have segregated the fundamental cause the precipitating causes and the underlying causes of congestive heart failure In considering the fundamental cause we attempted to investigate the *mechanism* or bridge by which the diseased and occasionally the normal heart becomes the failing heart The precipitating causes include the clinical conditions which because of their close sequential relationship appear to be concerned in the onset of the symptoms of heart failure The underlying causes of heart failure comprise those diseases which injure the pericardium myocardium valves or peripheral vessels and thereby bring about functional and anatomic changes in the heart or vascular system which eventually lead to cardiac failure In other words the underlying causes of heart failure are the various specific forms of cardiovascular *disease* as contrasted with the forms of cardiovascular *failure* These underlying causes are considered in detail in subsequent chapters in this book

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Chapter 7

CLINICAL AND PATHOLOGIC FEATURES OF CHRONIC (CONGESTIVE) HEART FAILURE

Congestive heart failure is essentially a *clinical* syndrome From the physiologic viewpoint heart failure represents an inability of the heart to maintain an adequate output But it is difficult to measure this disability in clinical practice Furthermore because of compensatory mechanisms the cardiac output may sometimes remain normal despite the presence of heart failure (Chapter 8) The manifestations of congestive heart failure are only exceptionally directly due to an inadequate cardiac output, as a rule they are the consequences of the compensatory mechanisms Congestive heart failure is defined and recognized by the presence of distinctive clinical features which are the subject of this chapter

LEFT SIDED HEART FAILURE

While the normal heart appears to act as a single pump the left and right chambers are really distinct anatomic and functional entities Under pathologic circumstances one side or even one chamber of the heart may fail while the other side is still functioning normally Sooner or later failure of one side of the heart places a strain on the remainder which eventually leads to generalized cardiac failure but for a variable period isolated left sided or isolated right sided heart failure may exist as a distinct and independent clinical syndrome

Failure of the left side of the heart is the most important and most common form of congestive heart failure encountered in medical practice The existence the pathogenesis and the clinical features of left sided heart failure were noted by Hope[38] and by a succession of French physicians [51] In recent years the importance of the syndrome of left ventricular failure was stressed and its clinical features described in this country by Pratt [84] White [104] Weiss and Robb [102] and others in France by Gallavardin[32] and by Lutembacher[53] and in England by Bedford [8]

CAUSES OF LEFT SIDED HEART FAILURE

Left ventricular failure results from those cardiovascular diseases which injure or strain the left ventricle, namely hypertension coronary artery disease aortic valvular disease and mitral regurgitation Rarely there are other causes In children acute rheumatic myocarditis and congenital cardiac lesions are the commonest causes of heart failure Bedford[8] observed 154 cases of left ventricular failure in 132 of which the failure was paroxysmal and in 22 persistent or terminal In the group of 132 111 patients suffered from hypertension associated in 43 with angina pectoris or coronary thrombosis 12 patients suffered from coronary disease without hypertension 21 suffered from aortic valvular disease There were only a few cases of syphilitic aortic insufficiency

Left atrial failure results from mitral stenosis which is almost invariably caused by rheumatic heart disease Mitral regurgitation causes both left ventricular and left atrial failure It is seen among earlier age groups than is left ventricular failure Left atrial failure is seen predominantly among females and left ventricular failure among males These and other factors in the etiology of left sided heart failure are related not to the heart failure itself but to underlying causative diseases For this reason details as to etiology should be sought in the chapters devoted to these diseases

PATHOLOGIC PHYSIOLOGY OF LEFT SIDED HEART FAILURE

The pathogenesis of heart failure and its pathologic physiology will be discussed in Chapter 8 The pathogenesis of *left sided*

heart failure is discussed on page 184 The pathogenesis of the individual symptoms is discussed in Chapter 9

Most of the manifestations of left sided heart failure result from the increased pulmonary blood volume and consequent engorgement of the lungs and from increased pulmonary capillary pressure (Chapter 9) Among the resulting physiologic disturbances are the rigidity and loss of elasticity which interfere with normal inspiratory and expiratory movements, reduction in vital capacity impairment of diffusion of oxygen and slowing of the pulmonary circulation The last is partly beneficial because it compensates for impaired diffusion by permitting a longer period for each unit of blood to absorb oxygen and release carbon dioxide

PATHOLOGY OF LEFT SIDED HEART FAILURE

The pathology of left sided heart failure is essentially the pathology of engorged lungs (passive congestion of the lungs) The lungs appear somewhat different when the engorgement results from left ventricular failure in hypertensive, coronary artery or aortic valvular disease than when it results from left atrial failure in cases of mitral stenosis The differences are due to the more gradual development and the much longer duration of the pulmonary engorgement with mitral stenosis The latter is described in detail in the chapter on mitral stenosis (p 26)

The lungs in left-sided heart failure are usually larger and firmer than normal, and do not collapse readily when the chest wall is opened because of increased content of blood and therefore diminished elasticity In cases of left ventricular failure the lung is usually dark red and "wet" in that bloody or frothy fluid may be expressed easily by squeezing or scraping of the surface or by cutting into the lung In cases of longstanding pulmonary congestion, e g, in mitral stenosis the lung is usually dry and indurated due to fibrosis and brown due to deposition of hemosiderin following phagocytosis of extravasated erythrocytes (brown induration of the lungs)

Microscopically[61] the lungs reveal engorgement and widening of capillaries with encroachment on alveoli, thickening of alveolar septa, extravasation of large mononuclear cells (heart failure cells) containing erythrocytes or the reddish granules of the iron pigment, hemosiderin

Other frequent findings in the lungs, besides pulmonary congestion and pulmonary edema, include pulmonary *emboli and infarcts hemorrhages*, hypostatic congestion, *bronchopneumonia* and bronchitis atelectasis and hydrothorax or pleural effusion There may be miliary, nodular aggregates of macrophages containing hemosiderin (p 643) The *pulmonary vessels* show medial hypertrophy and some intimal hyperplasia and fibrosis of the muscular arteries probably related to increased pulmonary vascular pressure[96a]

CLINICAL FEATURES OF LEFT SIDED HEART FAILURE

Symptoms

Exertional Dyspnea and Dyspnea at Rest Dyspnea (breathlessness, shortness of breath) denotes the subjective respiratory distress associated with increased effort in breathing When mild it may be purely subjective and discovered only by specific inquiry or from the patient's voluntary complaint When more severe there may be objective evidence of increased respiratory effort such as interrupted breathless speech, frequent stops during walking or climbing stairs dilatation of the alae nasi or, when very severe the use of the accessory muscles of respiration

Dyspnea during ordinary exertion is usually the earliest symptom of left-sided heart failure The dyspnea may be minimal in the morning and may progress gradually until it is quite disturbing by the time the patient retires at night (evening dyspnea[17]) At first dyspnea occurs only with moderately severe exertions such as running for a bus or train walking up a hill or climbing several flights of stairs Gradually, or more rapidly (e g, after an infection or coronary occlusion), the dyspnea becomes more severe and appears with less and less strenuous activity The patient then experiences breathlessness even when walking along level ground and is compelled to rest frequently in order to get his breath Finally dyspnea may persist even when the patient is at rest in bed

Of interest is the frequent alleviation of dyspnea when the right heart also fails Conversely in combined right- and left-sided heart failure the administration of digitalis and diuretics sometimes leads to an initial intensification of dyspnea as the mobilization of edema fluid and right ventricular improve-

ment lead to an augmented output into the pulmonary vascular tree

The subjective nature of mild dyspnea sometimes makes it difficult to evaluate Cardiac dyspnea is of a panting or puffing quality and not merely an "inability to take a deep breath The latter sometimes characterized as sighing respiration, is often of psychic origin Objectively cardiac dyspnea is characterized by rapid, shallow respirations in contrast with the deep breathing of diabetic or uremic acidosis The total ventilation per minute (rate times depth) is increased [64] The increase in ventilation is proportionately greater than the increase in oxygen consumption [64] When dyspnea is caused by heart failure it is precipitated by exertions previously performed without discomfort Factors such as increasing obesity, change to sedentary occupation, pregnancy, pulmonary disease etc, must be excluded

Pathogenesis of Dyspnea (see p 189)

Orthopnea Orthopnea is the form of dyspnea which occurs when the patient assumes a recumbent position To avoid respiratory distress on going to bed he elevates the head and chest with two or three pillows Sometimes he unconsciously adopts a semi sitting position while asleep When the orthopnea is severe the patient may have to be propped straight up in bed or he may obtain comfort only by sitting at the edge of the bed with his feet hanging, often his head and neck are flexed forward and his hands clutch the side of the mattress in order to aid the accessory muscles of respiration He may spend most or all of the night in a chair because this offers the best support and the least recumbency

These positions tend to relieve orthopnea by diminishing pulmonary congestion and improving pulmonary ventilation (p 191) In patients with continuous dyspnea and orthopnea breathlessness persists even after sitting up but it is usually less intense than in the recumbent position In some persons orthopnea occurs in one recumbent position (e g the left lateral) but not in another (e g the right lateral) This selective type of orthopnea, which has been termed trepopnea [103] is probably the result of greater pulmonary engorgement in the first position than in the other

Orthopnea may be noted at night in persons who have suffered no exertional dyspnea during the day I have seen patients with valvular heart disease who have had to sleep on two or three pillows at night because of orthopnea and yet continued for several years to conduct their business during the day without noticeable dyspnea

Pathogenesis of Orthopnea (see p 194)

Paroxysmal Dyspnea Paroxysmal dyspnea refers to the respiratory distress which appears in attacks without apparent cause Because such attacks usually occur at night after the patient has fallen asleep they are often called paroxysmal nocturnal dyspnea The term *cardiac asthma* is employed synonymously with paroxysmal dyspnea because the wheezing character of the respiration and the signs in the lungs resemble those in bronchial asthma Paroxysmal dyspnea usually occurs in patients who are suffering also from exertional dyspnea and from orthopnea Occasionally persons who are fairly comfortable and have little or no dyspnea during ordinary activity by day are intensely distressed by nocturnal dyspnea

The *attack of paroxysmal dyspnea* almost invariably occurs about an hour or two after the patient has retired and fallen asleep Diurnal attacks also occur while the patient is asleep The *precipitating cause* of the attack is uncertain and probably variable Cough bad dreams slipping of the patient from his pillows to a more recumbent position, turning to the side on which he is ordinarily dyspneic abdominal distention are among those suggested

The attack varies greatly in severity and duration In mild cases the patient awakens with a sense of respiratory distress or suffocation often associated with anxiety To obtain comfort he may merely sit up in bed or sit at the edge of the bed with his feet hanging In other instances the patient pleads to have the windows opened further or sits in a chair beside the open window because of the mistaken feeling that there is insufficient air in the room In the mildest cases relief is obtained a few minutes after sitting up Often the attack ends immediately after coughing up and expectorating blood tinged mucus In the less mild cases relief may not occur for half an hour to an hour In the relatively mild cases the physician may not be summoned at all or the attack may have subsided by the time the physician arrives

In severe attacks of paroxysmal nocturnal

dyspnea, the respiratory distress is much more intense and prolonged. The patient is found sitting upright in bed trying desperately to get more air by the use of the accessory muscles of respiration. The breathing is rapid. Sometimes it is noisy due either to audible asthmatic wheezes[83] or to bubbling or gurgling sounds caused by moisture in the lungs. As a rule the respiration is regular, but *it may have periodic variations. Occasionally* attacks follow each other in rapid succession—a cardiac form of status asthmaticus. The attack usually yields dramatically to a hypodermic injection of morphine and other therapeutic measures (see p. 292). The next morning the patient may feel as well as before the attack but more often he is exhausted and breathless. Occasionally a severe or protracted attack of paroxysmal nocturnal dyspnea ends fatally, usually with the development of extensive pulmonary edema. During the attack the circulation time is prolonged,[9] the pulmonary artery and capillary pressure are increased[49] and the systemic venous and right atrial pressure are increased,[85, 49] except in the presence of shock. The vital capacity is diminished.[102, 80] The arterial blood oxygen is often diminished,[79] but Vitale and associates[100] found an arterial oxygen saturation greater than 93 per cent in 7 of 12 patients with acute pulmonary edema.

Pathogenesis of Paroxysmal Dyspnea (see p. 195).

Pulmonary Edema. Clinical manifestations of pulmonary edema are usually observed in patients suffering from cardiac asthma. Often pulmonary edema accompanies or complicates the attacks of paroxysmal dyspnea. But it may appear for the first time in persons who have never experienced any form of dyspnea, e.g., after an attack of coronary artery occlusion, an hypertensive crisis, after exertion in patients with mitral stenosis, or after transfusions or intravenous infusions.[[illegible], 94] A slight degree of pulmonary edema is probably present during most attacks of cardiac asthma, but a characteristic clinical picture is produced only with massive edema of the lungs. Repeated nocturnal attacks of acute pulmonary edema may occur in patients who are asymptomatic and carry out normal activity and work during the day. Between attacks there may be no symptoms or signs of heart failure. Like cardiac asthma, pulmonary edema usually occurs in patients with left ventricular failure secondary to coronary artery disease (especially coronary occlusion), hypertension and aortic valvular disease. Pulmonary edema occurs less commonly with mitral stenosis, usually as a complication of pregnancy or labor, undue physical exertion, sexual intercourse, tachycardia or a pneumonic infection.

The clinical picture of acute pulmonary edema[46] is characterized by intense dyspnea, orthopnea, cough and extreme anxiety. The breathing is always noisy either because of loud inspiratory and expiratory wheezes or audible gurgling or bubbling sounds. There is always a fair amount of sputum but in severe attacks the patient drowns in the profuse secretions which may pour from the nose as well as the mouth. The sputum is usually frothy and may be colorless, but as a rule it is pink stained because of the presence of blood. The sputum is unusually rich in protein, the concentration of which may be as high as [illegible] to 3 per cent.

The patient is cyanotic, especially if the attack is prolonged, and often his skin is covered by a cold sweat. He may suffer from intense precordial oppression or actual pain. The blood pressure is usually elevated unless there is shock. The pulse is full but if relief is not obtained it becomes rapid and thready. As in cardiac asthma, the physical signs may resemble those of intense pulmonary emphysema. But whereas with cardiac asthma there may be no râles or sonorous, sibilant or crepitant rales at the extreme bases of the lungs, with definite pulmonary edema there are moist subcrepitant rales over extensive areas or throughout the lungs anteriorly and posteriorly. There are often also coarse bubbling râles which may be heard even without examining the patient.

The attack of pulmonary edema may be relatively mild or very severe. It usually subsides spontaneously after a few minutes or hours, often following the coughing up of some blood-stained frothy sputum. Frequently the attack is dramatically and rapidly controlled by an injection of morphine, the application of tourniquets to the extremities or a generous venesection. *Except for temporary exhaustion,* the patient is usually rapidly restored to the same condition as before the attack. While any given attack usually subsides spontaneously or with treatment, acute pulmonary edema

may end fatally in its first or some subsequent episode

Pathogenesis of Pulmonary Edema (see p 196)

Cheyne Stokes Respiration This is a periodic form of breathing characterized by waxing and waning of the depth of respiration and by regularly recurrent periods of apnea [17, 18] Left ventricular failure is most likely to be associated with Cheyne-Stokes respiration when it occurs in elderly persons with hypertension and cerebral arteriosclerosis who have received opiates or large doses of sedatives It may appear in association with the Stokes Adams syndrome It is not a specific symptom of heart failure and occurs in a variety of cerebral diseases Biot respiration, which is seen in patients with increased intracranial pressure is distinguished by identical depth of each respiration, irregular respiratory periods and only four or five breaths to each period [18]

In the typical Cheyne-Stokes respiration several hardly perceptible shallow respirations gradually and rhythmically deepen into respiratory excursions of normal depth After a half dozen such the respirations become deeper and deeper until they are abnormally exaggerated following which they again gradually subside until they are hardly perceptible This respiratory cycle comprising thirty or more respirations consists of phases of crescendo and diminuendo which occupy one to three minutes Often the shallow respirations shade off into a period of apnea which may last ten to thirty seconds or longer Prolonged apneic periods may be associated with deepening cyanosis and muscular twitchings of the face and extremities Cheyne-Stokes respiration may be accompanied by periodic changes in cardiac rhythm including sinus slowing nodal rhythm and various degrees of heart block

Pathogenesis of Cheyne-Stokes Respiration (see p 198)

Cough Cough is almost invariably present with the acute paroxysms of dyspnea and with pulmonary edema in patients with left sided heart failure It may also be a significant symptom in the intervals between such attacks It is often worst at night or occurs only at that time Insomnia may be due to the cough Sometimes the cough of heart failure like dyspnea may be induced only by exertion or recumbency The cough may be secondary to the pulmonary engorgement, to chronic congestion of the bronchial mucous membrane or to pulmonary infarction or bronchopneumonia Of special interest are instances of left heart failure in which cough dominates the symptomatology and dyspnea is overlooked I have frequently observed such patients treated for bronchopulmonary disease It is important to recognize that a bronchitis in elderly persons is often an evidence of congestive heart failure Fever may be absent or only of slight degree Harrison Calhoun and Harrison[17] have emphasized the significance of cough not only as a symptom of left sided heart failure but as a factor in precipitating cardiac asthma intensifying dyspnea when present, and in increasing the strain on the right ventricle by elevating the pulmonary arterial pressure

Cough is an important symptom in certain forms of cardiovascular disease, even in the absence of heart failure It is observed in cases of luetic aneurysm with compression of trachea or bronchus, of mitral stenosis with very large left atrium or pulmonary artery compressing a bronchus or of a congenital double aortic arch forming a vascular compression ring around the trachea (p 781)

The cough is usually accompanied by mucopurulent expectoration In attacks of cardiac asthma and pulmonary edema the sputum is characteristically frothy and pink due to the presence of small amounts of blood In cases of mitral stenosis with pulmonary congestion the sputum is often rusty because of its content of hemosiderin bearing 'heart failure cells' When infarction of the lung occurs in left sided heart failure the sputum is often extremely tenacious and blackish red or it may be frankly bloody

Hemoptysis The expectoration of blood or bloody sputum in mitral stenosis and pulmonary edema has been mentioned In the presence of heart failure it is often due to an associated pulmonary embolism and infarction

Cyanosis Cyanosis of mild degree is often present in pure left sided heart failure but it is not a characteristic feature It is an early and frequent symptom of the pulmonary congestion due to mitral stenosis Cyanosis may be prominent in left ventricular failure when there is acute pulmonary edema or when there are complications such as bronchopneumonia pulmonary embolization or a coincident pulmonary emphysema

Pathogenesis of Cyanosis (see p 204)

Hoarseness Hoarseness is a rare symptom of left sided heart failure and has been attributed to paralysis of the left recurrent laryngeal nerve as a result of compression by a dilated pulmonary artery [45]

Physical Signs of Left Sided Heart Failure

The Heart *Enlargement of the Heart* may be revealed by inspection and palpation of the apical impulse by percussion and by roentgenologic and electrocardiographic examination

Gallop Rhythm (p 68) Gallop rhythm is usually heard only or best near the apex of the heart but it may be present to the left of the lower sternum or occasionally in other parts of the precordium Since gallop rhythm is audible as a rule, only in the presence of tachycardia, it may be brought out by having *the patient exercise The gallop is most distinct* in deep expiration and with the patient on his left side As a rule gallop rhythm does not occur or disappears with atrial fibrillation[12] but there are exceptions

Pathogenesis of Gallop Rhythm (see p 69)

Accentuation of the Second Pulmonic Sound is due to the high tension in the pulmonary artery in left sided heart failure [10] The second pulmonic sound may become louder than the second aortic even when there is pronounced systemic hypertension

An Apical Systolic Murmur is frequently present due to a relative mitral insufficiency Tachycardia is frequent Tic tac sounds (embryocardia) may result from shortening of diastole by tachycardia with consequent even spacing of the two sounds *Atrial fibrillation* may be present

Cardiac Signs of the Underlying Disease These are discussed under the individual headings of hypertension, aortic stenosis, etc

Alternation of the Pulse may be a sign of left ventricular failure It is recognized by inflating *the cuff to the systolic pressure* As the cuff is very slowly deflated only alternate beats are heard for a distance of 2 to 10 or more mm Hg below the systolic level Rarely pulsus alternans is recognizable by palpation of the radial pulse unlike premature beats of pulsus bigeminus, the weak beat is very slightly closer to the succeeding beat than to the preceding one The heart sounds do not usually appear to be modified, but graphic records have demonstrated such alternation in intensity of the sounds[19] (Fig 53*A*) Alternation of the amplitude of contraction has been demonstrated by roentgen kymography[81] and electrokymography[21] Alternation of the QRS or T wave or of any other wave in the electrocardiogram may be associated with pulsus alternans This is termed electrical alternans (Fig 53*B*) It may be absent when the pulsus alternans is present or it may occur in the absence of pulsus alternans

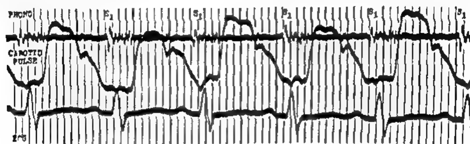
Pathogenesis of Pulsus Alternans (see p 206)

The Lungs *Basal Râles and Emphysema* Sometimes the signs are those of a functional emphysema, as noted particularly by Weiss and Robb [102] Between attacks of cardiac asthma or pulmonary edema, there may be no râles or only a few crepitant or subcrepitant râles at the bases of the lungs posteriorly *The most common signs in moderately* advanced left heart failure are râles at the bases of the lungs posteriorly The râles are occasionally unilateral or predominantly on one side During or immediately after an attack of cardiac asthma there may be many sonorous or sibilant râles resembling the rhonchi of bronchial asthma With pulmonary edema, fine and coarse moist rales become more extensive and the entire chest may be filled with bubbling or gurgling sounds In addition there may be signs of a complicating bronchitis bronchiectasis bronchopneumonia or pulmonary infarction hydrothorax or other pleural effusion Pulmonary infarcts are almost always bland and disappear completely But occasionally they undergo suppuration [77]

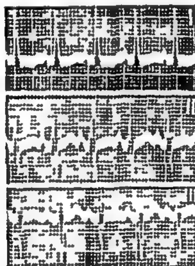
Hydrothorax According to Bedford[8] hydrothorax occurred in 25 per cent of his 154 cases of left-sided heart failure A pleural effusion which often contains blood may follow pulmonary infarction Unlike the fluid of hydrothorax this effusion has the characteristics of an exudate Occasionally an encapsulated interlobar effusion is seen[2] or multiple localized pleural effusions may occur[72] usually on the right side [103] A localized effusion in the oblique or transverse fissure *may simulate the roentgen appearance of a* neoplasm or other pulmonary lesion, its disappearance with vigorous therapeutic measures has given rise to the expression "vanishing tumor" of the lung [101] Often the inter*lobar effusion persists for some time after* other manifestations of heart failure are well

controlled The interlobar localization of the effusion has been attributed to a previous obliterative pleurisy which spared the fissure but sealed it off from the rest of the pleural cavity Recurring pleural effusion has been reported in two cases of massive left atrial thrombosis Usually hydrothorax in the course of congestive heart failure appears predominantly or exclusively on the right

rough parallel and no causal relationship (p 192) The vital capacity is the sum of the reserve, tidal and complemental air (p 972) and its reduction is the result of changes in one or more of these primary lung volumes The *reserve air* is usually diminished, denoting a loss of pulmonary elasticity The *tidal air* is also diminished when heart failure is moderately severe The *complemental air* (inspiratory



A



B

Fig 53 *A* Alternation in intensity of heart sounds and pulsus alternans Upper strip = phonocardiogram middle strip = carotid pulse lower strip = simultaneous electrocardiogram
B Electrical alternans Alternating variations in height of R and S waves best seen in lead III

side [57] but in Bedford's[3] cases of left sided heart failure the pleural effusion more often involved the left pleural cavity For further discussion see p 203

Lung Volumes

The *vital capacity* as well as the total pulmonary air space is greatly diminished in heart failure [78, 81, 102] The occurrence and severity of dyspnea has long been related to the reduction in vital capacity, but there is only a

capacity) is often markedly reduced indicating impaired distensibility of the lungs See also lung volumes in mitral stenosis (p 651) and in pulmonary emphysema (p 987)

In a study of 26 cardiac patients with low cardiac output, Richards et al [66] noted an increase in residual air and a reduction in complemental air even in compensated cases As definite congestive heart failure supervened complemental air was further reduced

and the reserve air was diminished. With extreme failure residual air was diminished and all lung volumes including vital capacity and total lung volume were decreased. They stressed the importance of increased heart size in producing these changes by encroaching on the thoracic space available for the lungs. On the other hand considerable evidence suggests that these alterations indicative of impaired elasticity and of impaired distensibility of the lungs in heart failure are due to rigidity caused by pulmonary vascular engorgement[7] or increased pulmonary capillary pressure.

Changes in lung volumes in heart failure

Roentgenologic Appearance of the Heart and Lungs in Left Sided Heart Failure[95a]

The *hilar shadow* is often increased both in density and width. Extremely wide (and pulsating) hilar shadows are also seen in cases of congenital heart disease such as interatrial septal defect, patent ductus arteriosus, in pulmonic valvular insufficiency, and occasionally in heart block.

The *lung fields* appear cloudy (Fig 54*A*) partly because of an accentuation and widening of the lung markings (i e the branches of the pulmonary vessels) and partly because of congestion, fibrosis or edema of the pulmonary tissue between the vessels.[69] The dense hilar



Fig 54 *A* Chronic venous congestion of the lungs in heart failure. Diffuse haziness of lung fields especially lower lobes. Prominent hilar vessels. Cardiac enlargement.
B Congestive heart failure with venous stasis in lower lobes and bilateral hydrothorax. Pulmonary infarct of right lower lobe may be obscured by pleural effusion.

depend on the nature of the underlying cardiac disease and the severity of heart failure and its pulmonary complication. Thus West, Bliss and colleagues[103] found no appreciable alterations in lung volumes in their patients with heart failure provided there was neither pulmonary edema nor hydrothorax.

The *increase in residual air* often present in congestive heart failure is similar to the finding in obstructive emphysema (p 987). Bronchial wheezes sometimes heard in heart failure especially during attacks of cardiac asthma also suggest the presence of bronchospasm in heart failure. As in obstructive emphysema there is a marked increase in uneven ventilation as measured by the elimination of pulmonary N_2 while breathing 99.6 per cent oxygen.[8]

shadows radiate in a fanlike fashion toward the periphery and particularly toward the base of the lungs. Where the engorged vessels run perpendicularly to the film they appear as conspicuous round shadows or nodular densities which may simulate miliary tuberculosis or carcinomatosis. Oblique views may disclose that these nodular densities are due to localized interlobar effusions.[70] There is often a diffuse haziness of the lung in its median and peripheral portions while the periphery is clear. Homogeneous mottled areas may result from alveolar exudation. Sometimes the homogeneous densities are indistinguishable from infarcts or consolidation. In pulmonary edema the shadows are usually widespread and symmetrical (Fig 55). Chronic pulmonary stasis with fibrosis and deposition of

hemosiderin produce nodular foci which may become calcified or rarely ossified (p 663)

Immediately after an attack of acute pulmonary edema there may be a cloudiness of the lung field in the area around the hilar shadows while the periphery of lung fields is clear [34] Then the shadow due to pulmonary edema extends to the bases The mechanism of this spread has been discussed by *Zdansky* [109] Free and encapsulated pleural effusions have been noted The roentgenologic picture of pulmonary engorgement may also be complicated by the coexistence of bronchopneumonia and pulmonary infarcts

The *cardiac silhouette* in left sided heart failure is determined chiefly by the underlying diseases for which the appropriate chapters should be consulted With the development of left sided heart failure there is evidence of progressive enlargement of the failing chambers With clearing of the heart failure the size of the heart is distinctly reduced

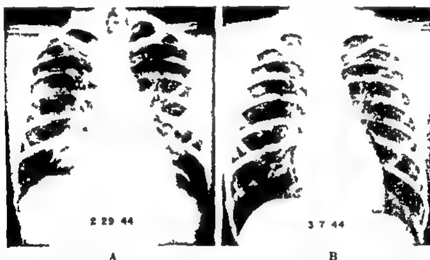


Fig 55 *A* Acute pulmonary edema in glomerulonephritis precipitated by intravenous infusions Exaggerated hilar and pulmonary markings Diffuse haziness especially of medial portions of lung fields with clearing at periphery and bases
B After recovery one week later

Circulatory Measurements

The *circulation time* is prolonged The arm to tongue time (p 213) exceeds 16 seconds the upper limit of normal and may be 40 seconds or more This is due to slowing of the blood stream in the dilated heart and in the congested lungs In the early stages of left sided failure the arm to lung time (ether) (p 215) may be normal indicating that the slowing is limited to the venous side of the pulmonary circulation and left cardiac chambers With frank left-sided failure both the arm to-lung and arm to-tongue time are prolonged

The *venous pressure* is normal in the absence of concomitant right sided heart failure

The *basal metabolic rate* may be slightly or greatly elevated (+15 to +60 per cent)[85] owing to excessive work of the muscles of respiration

The *arterial blood pressure* may be unchanged may fall or may become elevated (Hochdruckstauung[87 31]) depending in large measure on the underlying disease and the factors precipitating heart failure

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF LEFT SIDED HEART FAILURE

The diagnosis of left sided heart failure is made on the basis of the characteristic symptoms and signs of pulmonary congestion in a person with the types of cardiac disease which usually underlie left sided heart failure

The usual symptoms of pulmonary congestion are exertional dyspnea orthopnea paroxysmal dyspnea (cardiac asthma) pulmonary edema cough and hemoptysis The chief physical signs are râles at the bases of or throughout the lungs accentuation of the second pulmonic sound gallop rhythm and alternation of the pulse Many or all of these signs may be absent Roentgen ray examination reveals an enlarged heart prominence and widening of the hilar shadows and cloud

ing of the lung fields A prolonged circulation time is a valuable diagnostic confirmation

Differential diagnosis involves most often the distinction of left heart failure from bronchopulmonary disease as suggested by such symptoms as cough, dyspnea hemoptysis and asthma Roentgenograms of the chest physical and electrocardiographic examination to determine the presence of underlying cardiac disease and a careful history provide the needed data A prolonged circulation time distinguishes cardiac from bronchial asthma [72] Not infrequently a therapeutic test with the injection of one or more mercurial diuretics determines whether cough and/or dyspnea are due to cardiac failure or bronchopulmonary disease Dyspnea must be carefully evaluated to distinguish it from psychogenic disturbances in respiration

RIGHT-SIDED HEART FAILURE

Right-sided heart failure is most often combined with left sided heart failure In fact left sided heart failure with its associated pulmonary congestion and pulmonary hypertension, is the commonest cause of failure of the right ventricle Sometimes the entire heart fails simultaneously but the clinical features are predominantly those of right sided heart failure Occasionally, however, isolated right-sided heart failure is seen without left sided heart failure

CAUSES OF RIGHT SIDED HEART FAILURE

The underlying cardiac diseases which cause right-sided heart failure may be grouped as follows

1 Conditions associated with left sided heart failure and consequent pulmonary congestion and pulmonary hypertension which place a strain on the right ventricle Thus left-sided heart failure in essential hypertension, coronary artery disease and aortic and mitral valvular disease is followed usually in a few months or years by failure of the right ventricle

Under the heading of Bernheim's syndrome[8, 84] are included cases of pure right sided heart failure due to lesions such as hypertension or aortic stenosis which cause massive hypertrophy of the left ventricle including the interventricular septum The latter encroaches on the right ventricular chamber to such an extent that there is a functional obstruction to inflow into the right ventricle To satisfy the criteria for Bernheim's syndrome, left sided heart failure pulmonary disease or congenital cardiac lesions must be excluded as the possible cause of the right-sided heart failure The syndrome is not well established as an entity Selzer et al [83] have presented evidence based on hemodynamic studies with the aid of cardiac catheterization that cases of so called Bernheim s syndrome apparently represent instances of congestive heart failure in which dyspnea and other phenomena of left sided heart failure are inconspicuous, yet the catheterization findings are those of left-sided heart failure, pulmonary hypertension and right heart failure

2 Conditions which impair the function of the entire myocardium but which produce a predominant picture of right sided heart failure When the entire heart is affected, the right ventricle being weaker than the left fails more readily and the diminished output of the failing right ventricle spares the left ventricle e g rheumatic diphtheritic or toxic (Fiedler s) myocarditis severe anemias, beriberi and arteriovenous fistula

3 Primary diseases of the lungs, pulmonary vessels or pulmonic valve which cause strain and consequent failure of the right ventricle (cor pulmonale) (p 970) These instances of primary or isolated right ventricular failure are rare as compared with the cases of isolated left ventricular failure

4 Rare cases of predominant or isolated tricuspid stenosis cause failure of the right atrium and a clinical picture identical with that of right ventricular failure except for the signs of the primary disease

5 Conditions causing an obstruction to the inflow of blood into the right atrium such as constrictive pericarditis The resulting systemic venous engorgement produces a clinical picture like that with tricuspid stenosis in which there is a similar obstruction to inflow Prolonged ectopic tachycardias may also lead to right-sided heart failure

PATHOLOGIC PHYSIOLOGY OF RIGHT SIDED HEART FAILURE

This will be discussed in detail in Chapter 8 The symptoms of right sided heart failure are largely due to engorgement and elevation in pressure of the systemic veins and capillaries and the associated sodium water retention

PATHOLOGY OF RIGHT SIDED HEART FAILURE

Liver

The liver is dark red or brownish enlarged and firm because of chronic passive congestion[47] In cases of longstanding congestion it may undergo subsequent atrophy so that it is only slightly enlarged or even smaller than normal The term nutmeg liver refers to the appearance produced by the alternation of dark red and light brown areas The former is due to the central areas of venous congestion the latter to lesser congestion and the deposition of fat in the periphery of the lobule In the earliest phases of right sided heart failure with increased venous pressure there is dilatation of the central vein and sinusoids with narrowing of the liver cords Then there is centrolobular necrosis followed by capillary sclerosis and by organization and fibrosis of the central necrotic areas In addition poor nutrition may cause a fatty liver with diffuse fibrosis according to histologic studies of tissue obtained by needle biopsy[106] Eventually extensive fibrosis leads to *cyanotic induration* while necrosis and atrophy may cause *cyanotic atrophy* of the liver When the process of connective tissue formation and fibrous retraction is extensive the changes in the liver are described as cardiac cirrhosis[4] or cardiac fibrosis of the liver[64] Sclerosis of the hepatic veins[63] and of the superior vena cava[26] has been described, due presumably to the elevated pressure in these vessels during right sided heart failure The incidence of cardiac cirrhosis of the liver varies between 0 7 and 12 per cent of cases of heart failure depending on the criteria employed by different observers Cardiac cirrhosis is most likely to occur with multiple attacks of heart failure and especially when there is a very high hepatic venous pressure of prolonged duration I have observed it most often with functional or organic tricuspid stenosis and advanced right sided heart failure and with constrictive pericarditis The factor of an independent Laennec's cirrhosis is sometimes difficult to exclude Needle biopsy studies[106] may be helpful in making such diagnoses since clinical and laboratory data in heart failure are often inadequate to determine the character of associated hepatic disease But there is risk in needling the congested liver of heart failure

Peritoneal Cavity Gastrointestinal Tract Spleen and Pancreas

Increased capillary permeability and elevation of pressure in the peritoneal capillaries are the chief factors leading to the transudation of fluid and the appearance of variable and sometimes vast quantities of ascitic fluid in the peritoneal cavity Secondary infection of the ascitic fluid may cause inflammation and thickening of the peritoneum and of the peritoneal covering of the viscera especially the liver The hypertension of the portal circulation also causes passive congestion in the veins and capillaries of the entire gastrointestinal tract, with consequent edema thickening and occasionally hemorrhages

The *spleen* is enlarged dark red and firm (cyanotic induration), as a result of passive congestion and venocapillary hypertension of the portal (and hence of the splenic) circulation[43] According to Fowler[7] the spleen was sufficiently large to be theoretically palpable (i e over 300 gm) in 13 4 per cent of 97 cases of uncomplicated congestive heart failure and according to Wahi and Mathur[101] in 22 2 per cent The *pancreas* may also be the site of passive congestion

The Kidney

The kidney appears dark red and is firmer than usual because of chronic venous congestion The essential microscopic feature is the widening and engorgement of the intertubular veins and capillaries and usually also of the glomerular capillaries There is some proliferation of intertubular connective tissue but heart failure does not lead to significant fibrosis or contraction of the kidney

The Brain

Venous congestion with and without edema of the brain and leptomeninges, and alterations of the ganglion cells and nerve fibers have been described But the many cerebral symptoms seen in advanced heart failure are more probably due to severe cerebral arteriosclerosis sometimes with infarcts and encephalomalacia or to cerebral emboli arising in left atrial or ventricular thrombi

CLINICAL PICTURE OF RIGHT SIDED HEART FAILURE

Although the clinical pictures of right and left sided heart failure are sharply segregated for purposes of presentation and to emphasize their occurrence as isolated syndromes it

must be remembered that the symptoms of left and right sided heart failure are usually combined sooner or later, and often they appear almost simultaneously

Symptoms and Signs of Right Sided Heart Failure

The Heart and Lungs In the usual case of right-sided heart failure, the left heart is also insufficient and the signs in the heart and lungs are essentially those described under left-sided heart failure (p 146)

Cardiac enlargement is more pronounced and more universal than in pure left heart failure Roentgenograms may disclose definite enlargement of the right ventricle and atrium The shadows of the superior and inferior venae cavae become more distinctive The entire cardiac silhouette becomes enlarged to the left and right encroaching on both pulmonary fields and somewhat obliterating the individual cardiac contours There are insufficient comparative studies of the size of the heart but a few series indicate that the cardiac silhouette often undergoes distinct enlargement with failure and a diminution in size following recovery [74, 20] Comparisons are often difficult because of differences in technique and changes in the position of the diaphragm at the respective examinations during failure and in its absence

In cases of pure right sided heart failure secondary to intrinsic pulmonary disease, enlargement of the heart is often difficult to demonstrate There may be an enlargement only in the anteroposterior diameter or enlargement of the right chambers may be demonstrable in oblique views (p 105)

In combined right and left heart failure, râles at the pulmonary bases persist Hydrothorax occurs commonly especially on the right side or bilaterally Clouding of the medial and lower lung fields is frequently observed on roentgenologic examination Pulmonary infarction is common and may be associated with pleural effusion In cases of pure right sided heart failure due to pulmonary disease the roentgenologic findings in the lungs are those of the underlying pulmonary disease In cases of tricuspid stenosis and constrictive pericarditis with failure, the pulmonary fields are sometimes remarkably clear but hydrothorax is frequent

The *electrocardiogram* is not characteristic and is determined by the underlying disease or by complicating arrhythmias especially atrial fibrillation Prolongation of the QT interval is usual [16]

Subcutaneous Edema Edema, or the demonstrable accumulation of excessive fluid in the subcutaneous tissues, is a classic feature of right sided heart failure Usually it appears in a cardiac patient who has been suffering for months or years from dyspnea on exertion, orthopnea or cardiac asthma Occasionally a patient with heart disease who has never noted any of the above symptoms begins to complain of swelling of the feet or ankles which usually appears in the evening and subsides after a night's rest in bed A considerable amount of fluid may accumulate in the subcutaneous tissues before edema becomes apparent (invisible edema) This may be noted as an increase in body weight Conversely, the loss of invisible edema fluid may cause a reduction in weight and a continued diuresis after all visible edema has disappeared

The edema may occur in any part of the body, but because its localization is determined chiefly by an elevated hydrostatic capillary pressure, it is usually found in dependent parts of the body such as the feet, ankles (especially the inner malleoli), and pretibial region In a patient who has been in bed for some days or longer the edema is most prominent over the sacral region and may be overlooked unless this part of the body, which is now the most dependent, is carefully examined In patients with hemiplegia the edema is most conspicuous on the paralyzed side [78] Sometimes there is generalized, massive edema (anasarca) affecting all parts of the body including the genitalia, chest wall, arms and rarely, the face In the primary forms of right ventricular failure, in which orthopnea is usually absent and the patient sleeps in the recumbent position, there may be edema of the face or eyelids on arising But as a rule, edema of the face should suggest a renal etiology or some obstruction of the superior vena cava (Pathogenesis, see p 199)

Ascites Ascites or effusion of serous fluid into the abdominal cavity is the result of engorgement in the portal venous tributaries As a rule it is a later development and a less prominent feature than subcutaneous edema but in some forms of right sided heart failure (with tricuspid stenosis or constrictive pericarditis) there is considerable ascites with little edema There is also a group of cases of predominant right sided heart failure in

which ascites with little or with moderate peripheral edema follows shortly after an acute myocardial infarction The explanation for the early and outstanding ascites is uncertain It has been attributed to underlying cirrhosis of the liver or to infarction of the interventricular septum with consequent Bernheim's syndrome

The ascites may cause no subjective symptoms or the patient may notice only an increase in his abdominal girth Sometimes it leads to abdominal distention and distress or even to abdominal pain The ascites is often persistent and may recur repeatedly after aspiration In cases of constrictive pericarditis persistent and recurrent ascites is a characteristic feature (Pathogenesis see p 203)

Hydrothorax and Hydropericardium Subcutaneous edema and ascites are often associated with effusions into the pleural cavity (hydrothorax) (Fig 54*B*) and sometimes into the pericardial cavity (hydropericardium) to form the complete picture of cardiac dropsy Hydrothorax has been mentioned as occurring in left sided heart failure (p 146) as well as in right sided heart failure since the pleura drains into the pulmonary as well as into the systemic veins The pleural effusions in right-sided heart failure occur most often in the right pleural cavity or are most extensive on that side when there are bilateral effusions In left sided heart failure with regular rhythm the effusions according to Bedford and Lovibond[4] are usually on the left side but this has been questioned[47]

Pathogenesis of Hydrothorax (see p 203)

Usually pleural effusions are absorbed as heart failure improves but interlobar effusions are sometimes persistent (p 146) The chief effect of hydrothorax is to produce dyspnea or more often to exacerbate the dyspnea present by compressing the lung by diminishing its vital capacity and by reflex stimulation of breathing

Engorgement of Superficial Veins The large cervical veins and those on the dorsum of the hand may appear full and prominent In cases of advanced heart failure there may be pulsations of the superficial veins of the extremities[44] The retinal[49] and lingual veins[44] may also be conspicuously engorged with right sided heart failure

The normal pulsations of the cervical veins are best seen over the jugular bulb in the root of the neck with the patient supine In cases of right-sided heart failure the veins may become too distended to pulsate when the patient is supine As his head is gradually elevated a point of intense venous pulsation is reached Normally the cervical veins appear empty when a person is erect with severe right-sided heart failure these veins appear extremely engorged and their pulsations may be prominent The positive form of venous pulse (p 72) may be seen if there is associated atrial fibrillation or tricuspid insufficiency

Prominence of the superficial veins is an early sign of right-sided heart failure and may be noticeable before there is detectable subcutaneous edema, hepatic enlargement or other signs of heart failure This sign may persist even after rest in bed diuretics and other therapeutic measures have eliminated the edema Occasionally engorgement of the superficial cervical veins is revealed only by pressure over the right upper quadrant of the abdomen (hepato-jugular reflux) (infra) It is important to remember that in right-sided heart failure engorgement occurs in the tributaries of both the superior and inferior venae cavae When venous congestion is limited to the upper or lower portions of the body, some local venous obstruction should be sought

Enlargement and Tenderness of the Liver The enlarged liver can almost invariably be palpated clinically Its lower border may extend to the level of the umbilicus Hepatic enlargement is often present long before there is edema In infants and young children rapid enlargement of the liver is often the outstanding sign of cardiac failure while pulmonary signs and edema are often absent The liver often remains enlarged when all other symptoms of right sided heart failure have disappeared Often there is abdominal tenderness in the hepatic region due presumably to tension of the liver capsule With severe heart failure especially if there is significant tricuspid valvular insufficiency the liver pulsates synchronously with the right ventricular pulsations (see p 713)

The large liver may not only be tender on pressure but may cause spontaneous abdominal pain and this may be induced or intensified by exertion The abdominal pain rarely simulates that of cholelithiasis or cholecystitis Mild abdominal pain in patients with congestive heart failure may also be due to intense distention resulting from gastrointestinal disturbances (p 155) or ascites

Abdominal pressure over the engorged liver causes or increases visible engorgement of the cervical veins and a rise in venous pressure This phenomenon, known as the hepato jugular reflux is a diagnostic sign of right-sided heart failure and helps differentiate hepatic enlargement due to venous engorgement from that due to other conditions Hepatic or abdominal compression increases the venous return and intensifies the stasis in the cervical veins, owing to the inability of the failing right heart to handle the increased blood flow [24, 95]

Liver Function and Jaundice Hepatic congestion is often associated with a disturbance in the function of the liver [15] The latter is attributed to cellular hypoxia associated with an inadequate blood flow[68] and slowing of the blood stream as well as to cellular necrosis and atrophy secondary to venous congestion and hypertension Urobilinogen in the urine is increased [15] Hyperbilirubinemia is frequently present with right sided heart failure due to an increase in the direct and indirect (slow-reacting), bilirubin, especially the latter [89] Frank jaundice occurs in 2 to 5 per cent of the cases [46] The patients with jaundice usually suffer from combined left and right sided heart failure and have pulmonary infarcts as well as an engorged liver But jaundice may occur in the absence of infarction [76] In edematous areas the skin may not be jaundiced because the bile pigments do not enter into the edema fluid[88] or only to a slight extent,[1] possibly because of its low content of protein Jolliffe[43] found impairment of hepatic function indicated by excessive retention of injected bromsulfalein in 12 of 16 patients with right sided heart failure and similar findings have been reported by others [26, 95, 25] The van den Bergh reaction is positive There is some uncertainty whether the abnormal bromsulfalein test in cases of congestive heart failure actually denotes hepatic damage or is due entirely to circulatory stasis

The thymol turbidity test was abnormal in 31 per cent and the cephalin flocculation test in 22 per cent of the determinations made by Felder et al [6] in 135 cases of chronic protracted congestive heart failure They also noted an elevation of the alkaline phosphatase in 46 per cent of the determinations and in 83 per cent of the cases of cardiac cirrhosis studied at autopsy Although reported measurements of prothrombin time in congestive heart failure are not in universal agreement there appears to be a tendency to slight prolongation in prothrombin time and increased sensitivity to anticoagulants which act on the prothrombin [8] Deficient clearance of bromsulfalein has been attributed to slowing of the hepatic blood flow [67] but Sherlock[95] does not agree with this interpretation

Hepatic hypoglycemia has been said to occur much more often in congestive heart failure than is realized and has been held responsible for weakness, sweating, palpitation nervousness, irrational behavior and even convulsions or coma [59] Sudden but transitory improvement has been attributed to the intravenous administration of small doses of concentrated glucose solutions

Splenomegaly is found post mortem in 13 to 22 per cent of cases (p 151) but is only occasionally noted clinically Splenic enlargement was reported in 5 of 206 cases of congestive heart failure by Ibrahim et al [89]

Pathogenesis of Jaundice in Heart Failure (p 205)

Cyanosis A bluish discoloration of the skin and mucous membranes due to an excessive concentration of reduced hemoglobin in the blood is almost always seen in patients with right-sided heart failure It occurs most often and is most intense in the cases in which heart failure is secondary to pulmonary diseases or to congenital cardiac lesions causing a considerable admixture of arterial and venous blood When right sided heart failure complicates left sided heart failure dyspnea may be alleviated but cyanosis may appear or become intensified In left sided heart failure the severity of dyspnea is usually out of proportion to the cyanosis in right sided heart failure due to pulmonary lesions the cyanosis is often more prominent than the dyspnea

Pathogenesis of Cyanosis (p 204)

Fever usually denotes associated pulmonary infarction or bronchopneumonia or it may be due to rheumatic activity bacterial endocarditis or some other infection

Weakness may be a prominent symptom in advanced failure and is sometimes associated with extreme loss of weight and anemia (cardiac cachexia) It may be related to marked reduction in cardiac output to the increased work of respiration, to excessive diuresis or electrolyte disturbance, to nutritional deficiency, to associated cerebral, renal

or pulmonary disease to infection or to drug toxicity

Gastrointestinal Disturbances. Owing to venous engorgement anorexia and abdominal distention or a sense of fullness after meals are frequent Many gastrointestinal symptoms especially anorexia nausea and vomiting may occur not because of passive congestion but because of digitalis morphine or drugs The combination of meteorism with hepatic enlargement (and sometimes also ascites) may cause intense abdominal tension or even pain Constipation is sometimes distressing, more rarely there is diarrhea Intestinal bleeding is occasionally observed

Disturbances of the Nervous System Aphasia, paralyses convulsions and coma may be due to a complicating cerebral embolism with infarction and encephalomalacia The embolism arises from a thrombus in the left atrial appendage in cases of mitral stenosis or coronary heart disease and atrial fibrillation or on the wall of the left ventricle over the site of infarcation or aneurysm

There are numerous neurasthenic neurotic or psychotic manifestations which may or may not be directly related to the cardiac failure Scheinberg[70] measured the cerebral blood flow in congestive heart failure by the nitrous oxide method and found a reduction of 39 per cent associated with a marked rise in cerebrovascular resistance Similarly Moyer et al [65] noted a 20 per cent reduction in cerebral flow and increased cerebrovascular resistance However, Novack and associates[71] concluded that the reduction in cerebral blood flow was not due to the heart failure itself but to associated cerebral arteriosclerosis, since the cerebral blood flow in heart failure did not differ significantly from that in a control group of subjects chiefly between the ages of 50 and 70 presumably with cerebral arteriosclerosis without heart failure Similarly, a reduced cerebral oxygen consumption was attributed to older age and arteriosclerosis not heart failure These findings were interpreted to indicate that cerebral blood flow and cerebral metabolism (oxygen) tend to be maintained in heart failure despite a reduction in the cardiac output It is questionable therefore whether cerebral symptoms are due to heart failure itself except when the latter is very severe Headache is a common symptom Insomnia and bad dreams or nightmares are sometimes very distressing Hypochrondriasis and depression may be due to the patient's knowledge that he is suffering from heart disease or heart failure Occasionally there are true psychoses with disorientation, delirium hallucinations and delusions especially of a paranoid type [34] Psychotic symptoms as well as pronounced weakness may follow extreme diuresis after mercurial drugs Morphine and barbiturates are frequently contributory causes of mental symptoms Psychotic symptoms may be due also to digitalis intoxication or ammonium chloride acidosis to diarrhea to associated renal insufficiency pulmonary embolism bronchopneumonia or cerebral arteriosclerosis or to marked aberration in the blood electrolyte pattern In most cases of uncomplicated heart failure mental symptoms are absent

Renal Symptoms. *Nocturia* occurs frequently and may be due to an associated prostatic enlargement to the elimination of occult edema fluid when the patient is recumbent or to irritation of the bladder or urethra by concentrated urine Temporary anuria may follow active diuresis

Oliguria is a characteristic feature of right sided heart failure Since the diminution in urinary output parallels the severity of the heart failure, the urinary volume is usually a good index of progress When improvement occurs the volume increases with spontaneous or therapeutic diuresis a polyuria of 2 5 to 4 liters daily may appear

Urinary Findings

The *urine* is concentrated and has a *high specific gravity* usually between 1 025 and 1 030 However its sodium content is minimal [12, 80] When cardiac edema disappears as a result of spontaneous or therapeutic diuresis the specific gravity may be very low but the content of sodium and chlorides is increased The specific gravity of the urine may also remain low if cardiac failure complicates renal insufficiency or following frequent mercurial diuretics or prolonged and extreme restriction of sodium intake

Albuminuria is a common occurrence with congestive heart failure [84] Usually the albuminuria is slight, the concentration being less than 1 per cent and the daily excretion of albumin less than 1 gram Hyaline casts and sometimes granular and epithelial casts accompany the albuminuria Renal function as determined by urea clearance and PSP tests is usually depressed [11] (See also p 171)

The Erythrocyte Sedimentation Rate

It is widely believed that an increased sedimentation rate of erythrocytes falls to normal in the presence of congestive heart failure, notably in active rheumatic fever with heart failure[9] (p 835) But recent observations in 38 patients with congestive heart failure, before and after compensation was regained, disclosed that the majority of such patients exhibited elevated values, not only initially but after recovery as well[65]

Blood Chemistry

The *chemistry of the blood* may be altered Moderate *azotemia* (urea nitrogen between 20 and 40 mg per 100 cc blood) has been noted when there is severe oliguria Vigorous mercurial diuresis *may result in increasing azotemia despite a large urinary output*[30] Occasionally there is *hypoproteinemia*, the reduction being confined essentially to serum albumin Hypoproteinemia is most likely to occur after prolonged cardiac failure as a result of malnutrition, impaired hepatic formation of albumin, and perhaps also of a long continued loss of albumin in the urine and *in serous effusions The serum globulin* tends to be elevated[25] The arterial oxygen saturation is normal in many cases and almost always is above 90 per cent[83, 82] However a significant reduction in arterial oxygen tension accompanies even slight reductions in oxygen saturation in this range of the dissociation curve of oxyhemoglobin The venous oxygen in mixed venous blood in hepatic and in renal *venous blood is markedly reduced* and the respective arteriovenous oxygen differences are increased The arterial carbon dioxide content is normal or somewhat diminished as a result of hyperventilation The concentration of ammonia may be elevated and may account for cerebral symptoms[8]

Blood Electrolytes (See also pp 168 275)

The *concentration of sodium* in the plasma is usually diminished despite the reduction in urinary sodium[29, 61] It appears to be related chiefly to the low sodium intake of patients under treatment for congestive heart failure at the same time that they are receiving mercurial diuretics Indirect evidence suggests that the reduction in plasma sodium may be due in part also to the passage of significant amounts of this ion into the cells[29] On the other hand recovery from heart failure is associated with a restoration of plasma sodium to normal concentration

In general plasma chlorides behave like sodium Like the latter, chlorides are poorly excreted in the urine, but there is often a quantitative dissociation The concentration of chlorides may be diminished as a result of mercurial diuresis or as a result *of associated* pulmonary emphysema with carbon dioxide retention Under both circumstances bicarbonate concentration is increased, but in the former there is alkalosis, in the latter acidosis The concentration of chlorides may be increased and that of bicarbonate and hydrogen ions diminished (hyperchloremic acidosis) as a result of diuretics such as am*monium chloride or Diamox or resins,* while *the concentration of the sodium is normal* In advanced heart failure in the presence of marked renal impairment or as a result of extreme restriction of sodium intake both chloride and sodium concentrations may be greatly reduced

The *plasma potassium* is relatively normal but balance studies during recovery from *heart failure*[14] *and studies of potassium excre*tion following diuretics[8] suggest that this essentially intracellular ion may undergo significant shifts out of the cell Studies with radioactive K^{42} suggest that total body potassium is diminished in congestive heart failure even though the plasma (extracellular) potassium concentration is normal[14] The potassium concentration is usually somewhat reduced in cases with hypochloremic alkalosis caused by mercurial diuresis

Chiefly as a result of therapeutic measures but also because of complicating renal or pulmonary disease a variety of abnormal blood electrolyte patterns may be observed These are discussed in more detail in Chapter 11 *in connection with various therapeutic* measures

Circulatory Measurements (See Chap 10) The *circulation time is prolonged* (p 167)

The *blood volume* is augmented[22, 60] (p 166)

The *venous pressure* is elevated in contrast with the normal venous pressure of pure left *sided heart failure (p 165)*

The *cerebrospinal fluid pressure* is determined by the venous pressure and is elevated in cases of right sided heart failure

The *arterial blood pressure* undergoes no characteristic change

DIAGNOSIS OF RIGHT SIDED HEART FAILURE

The diagnosis of right-sided heart failure is usually simple in patients with known cardiac disease or with preceding left sided heart failure The combination of enlarged heart congested cervical and peripheral veins subcutaneous edema of the dependent parts, and hepatic enlargement usually suffices to make the diagnosis An elevation of venous pressure with or without pressure over the right upper quadrant of the abdomen is confirmatory In incipient right-sided heart failure the venous pressure may not be elevated However the tendency to systemic congestion may be demonstrated by the hepato-jugular reflux or by a rise in venous pressure following simple leg exercise Normally there is no rise in *venous pressure*

I have often seen middle-aged and usually obese women who complain of shortness of breath and swelling of the ankles because of which they were told their hearts were failing Study usually revealed that the dyspnea was due to lack of exercise and obesity or that it was merely a psychogenic inability "to take a full breath" or a tendency to sighing respiration The edema was usually hypostatic due to flat feet varicose veins obesity and prolonged standing That these individuals are not suffering from heart failure can be proven by the exclusion of underlying hypertension or heart disease, with roentgen ray examination of the chest and electrocardiography and by the finding of a normal venous pressure and normal circulation time

Differential diagnosis involves the differentiation between heart failure and the multiplicity of pulmonary renal hematologic hepatic and abdominal or thoracic diseases *which may produce dyspnea edema* venous engorgement cough hepatic enlargement, hydrothorax or pleural effusion or ascites In the presence of ascites with advanced heart failure it is necessary to differentiate tricuspid stenosis constrictive pericarditis and cirrhosis of the liver

If heart failure is present it should be possible to demonstrate some underlying causative cardiovascular disease Cardiac enlargement should be demonstrable except with constrictive pericarditis If the right heart has failed *the physician should demonstrate that* the venous engorgement and elevation of venous pressure concern both the superior and inferior caval systems and not merely one or the other A prolonged circulation time is diagnostic of heart failure in the absence of polycythemia vera On the other hand, fever severe anemia, hyperthyroidism beriberi severe emphysema and arteriovenous aneurysm tend to restore the prolonged circulation time of heart failure to within the normal range Sometimes the diagnosis of congestive heart failure is finally confirmed by a satisfactory response to digitalization low sodium intake and the exhibition of mercurial diuretics

FUNCTIONAL CLASSIFICATION OF HEART DISEASE (SEVERITY OF HEART FAILURE)

The New York Heart Association set up a classification of patients with congestive heart failure *which has proved useful in evaluating* their functional status and in prognosis In the latter connection the classification has been used in the study of the cardiac patient and pregnancy and of patients submitted to mitral commissurotomy The classification is based essentially on the patient's symptoms during various grades of activity Hence its value is limited by its dependence on the subjective reaction of the patient Self imposed or physician imposed inactivity and psychic factors as well as the cardiac status may influence this reaction

Class I Patients with cardiac disease but with *no limitation of physical activity* Ordinary physical activity causes no undue dyspnea, anginal pain fatigue or palpitation

Class II Patients with slight limitation of physical activity They are comfortable at rest and with mild exertion They experience symptoms only with the more strenuous grades of ordinary activity

Class III Patients with marked limitation of physical activity They are comfortable at rest, but experience symptoms even with the milder forms of ordinary activity

Class IV Patients with inability to carry on any physical activity without discomfort Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest and are intensified by activity

COMPLICATIONS OF CONGESTIVE HEART FAILURE

The complications of congestive heart failure are those associated with the underlying cardiac disease those related to congestion or elevated venocapillary pressure in various

tissues or organs and those due to therapeutic measures and to intercurrent disease

Venous thrombosis in the lower extremities and subsequent pulmonary embolism are among the most frequent and most serious complications of congestive heart failure Pulmonary embolism may be associated with infarction and distinct clinical symptoms such as chest pain cough hemoptysis and fever But often there are only non localizing manifestations such as fever weakness, transient dyspnea or cyanosis or tachycardia restless ness and anxiety and these are overshadowed by the manifestations of heart failure itself Commonly the heart failure is intensified or is refractory to treatment because of recurrent pulmonary embolism

Pulmonary emboli may also arise from thrombi in the right atrium especially in patients with atrial fibrillation and heart failure In idiopathic forms of heart failure pulmonary emboli arise from mural thrombi in the right ventricle (p 624)

Arterial emboli may occur as a result of mural left ventricular thrombi in cases of coronary heart disease or from the left atrium in cases of heart failure with atrial fibrillation

Rarely venous thrombosis in the upper extremities occurs as a complication of cardiac failure Loring[5] collected 83 cases from the literature and added four additional cases Furthermore such venous thrombosis may be complicated by pulmonary emboli and infarction, as in the six cases reported by Tomlin ■

The variety of other pulmonary complications besides embolism and infarction have been mentioned notably bronchopneumonia, pleural effusion and pulmonary edema

Other complications include cerebral vascular insufficiency cerebral thrombosis or embolism renal insufficiency cardiac cirrhosis colitis, bacterial endocarditis digitalis toxicity and disturbances in plasma electrolyte pattern

COURSE AND PROGNOSIS OF CONGESTIVE HEART FAILURE

The course and cause of death in congestive heart failure are often determined or modified by the underlying cardiac disease Death is often precipitated by a pulmonary or cerebral embolism and infarction or by an acute coronary occlusion Acute pulmonary edema is a frequent form of termination In their analysis of the causes of death in 185 patients with congestive heart failure, Williams and Rainey[107] emphasized the relative increase in importance of fatal pneumonias Since their study the liberal use of sulfonamides and antibiotics has sharply reduced the incidence of fatal pneumonia Uremia is fairly common as a cause of death in patients with malignant hypertension or nephritis and heart failure

Left sided heart failure ■ often variable in its course and duration I have known cardiac patients who have suffered from exertional dyspnea and slight orthopnea for ten or more years before the symptoms of right sided heart failure developed In patients with mitral stenosis mild symptoms of pulmonary congestion are almost part of the disease itself, for they occur early and may last many years before the patient is unable to carry on his normal activities However in the presence of dyspnea on slight exertion or at rest, repeated attacks of cardiac asthma recurrent pulmonary edema alternation of the pulse or persistent gallop rhythm, the outlook is usually unfavorable

Most of the studies on prognosis in heart failure state that the duration of life in cardiac disease complicated by right heart failure is only one to two years and rarely up to five Grant[35] found the average duration of life in the presence of venous congestion was two and ■ half years Williams and Rainey[107] found that in the period between 1931 and 1935 patients hospitalized with congestive heart failure due to rheumatic heart disease lived 32 months, those with arteriosclerotic heart disease 40 months and those with luetic heart disease 11 months But in recent years I have seen many patients who have survived five to ten years or more after the development of right-sided heart failure This is undoubtedly due to judicious restriction of sodium and administration of mercurial diuretics in the past twenty years

In general the outlook is relatively favorable if the symptoms of congestive failure subside rapidly and completely with appropriate treatment The less intense and prolonged the required treatment before recovery ■ effected, the more probable is the persistence of recovery

An important clue as to the patient's course ■ obtained from a study of his renal excretion of sodium and his response to the in

gestion of moderate amounts of sodium chloride[39] Some patients excrete sodium fairly well after disappearance of their symptoms of heart failure and there is no recurrence of symptoms or evidence of water retention following the daily ingestion of 5 to 10 gm of sodium chloride for five days As a rule heart failure in these patients was induced by an infection a pulmonary infarct anemia or some other factor which subsided or was eliminated by treatment These patients have a relatively good immediate prognosis and their hearts remain compensated with little or no sodium restriction and without the use of mercurial diuretics

At the other extreme is a host of patients who even after vigorous treatment and control of overt symptoms excrete almost no sodium in the urine and promptly experience a retention of fluid and recurrence of symptoms following the ingestion of as little as 1 to 2 gm of sodium chloride daily Heart failure in these patients can only be controlled by extreme sodium restriction and the frequent administration of mercurial diuretics in addition to other therapeutic measures Other patients fall between these two extremes their outlook for maintenance of clinical improvement may be graded according to their renal excretion of sodium and their response to the ingestion of sodium chloride

The outlook is relatively better if there is an obvious precipitating factor which can be eliminated than if congestive heart failure appears without any apparent immediate cause or as a result of one which cannot be treated Sodeman and Burch[37] found that of 47 patients in whom congestive heart failure appeared gradually and without apparent precipitating cause 16 were unable in spite of treatment to compensate sufficiently to carry on minimal normal activity On the other hand in 54 patients with a demonstrable precipitating cause for congestive heart failure compensation was established rapidly under treatment so that the patient could resume his activities

The outlook is also relatively better in the well to-do than in persons of low economic level Cooperation and intelligent execution of the physician s orders by the patient and his family also improve the outlook The prognosis in any given case of congestive heart failure should be guarded even when it appears relatively favorable because of the danger of serious complications or sudden death

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Chapter 8

THE PATHOGENESIS OF CHRONIC CONGESTIVE HEART FAILURE

Chronic congestive heart [illegible] pro longed impairment of th[illegible] the heart to maintain an adequa[illegible] to the tissues. The manner in [illegible] ability arises was discussed in [illegible] on the etiology of heart failure. [illegible] concerned here with the mechanism [illegible] which such cardiac impairment lea[illegible] manifesta tions of congestive heart [illegible]

PATHOLOGIC PHYSIOLOGY OF HEART FAILURE

The disturbances in physiology of the circulation are characterized by: (1) Alterations in circulatory dynamics, particularly in blood flow and in pressure relationships throughout the cardiovascular system. (2) Abnormalities in fluids and electrolytes, particularly in the quantity and distribution of body water and in the total body content and concentrations of sodium.

ALTERATIONS IN CIRCULATORY DYNAMICS

The Cardiac Output in Congestive Heart Failure

Since the function of the heart is to provide an output of blood which is adequate for bodily needs throughout the range of physiologic activity, heart failure may be defined to indicate that the output is no longer adequate. But there is no direct method of determining body needs or the adequacy of the blood flow for these needs. Demonstration of a deficiency of cardiac output relative to body needs depends on the presence either of certain clinical symptoms or of disturbances in circulatory hemodynamics. The determination of cardiac output even under basal conditions presents technical difficulties (p 209). These are increased when cardiac output is determined during exercise. Furthermore we do not have satisfactory normal standards to indicate what the cardiac output should be for the variety of stresses to which the body is ordinarily subjected in the course of its physiologic activities.

Available determinations of cardiac output in congestive heart failure represent chiefly cardiac outputs with the subject at rest. Most investigators have noted at least a small diminution in cardiac output in the majority of cases of congestive heart failure. Earlier determinations of the cardiac output by the dye method[41], by the acetylene method[46, 47, 11, 114] and by physical methods[133] all showed that the cardiac output was usually reduced in groups of cases of severe heart failure, but there was often no significant reduction in cardiac output in patients with mild heart failure, and there was some overlapping of the values of cardiac output in patients with congestive heart failure and those with compensated heart disease as well as in normal persons. The accuracy of some of the methods used has been questioned, and indeed recent use of the more accurate direct Fick method (p 209) has disclosed more distinct reductions in cardiac output in heart failure than those determined previously[98, 74, 100, 141] but even among the more recent observations there are normal cardiac outputs in some patients with mild grades of heart failure.

It is difficult to define mild heart failure when applying the term to a given patient. Usage has not clarified the distinction between the expressions diminished cardiac reserve and heart failure, nor have we evolved satisfactory criteria for sharply defining the stage at which diminishing reserve is actually heart failure. The patient with rheumatic cardiovalvular disease who is generally regarded as well compensated, i.e. not in failure, can usually be shown to have a diminished cardiac reserve as compared with

his normal fellow, when he is subjected to severe or prolonged forms of physical exertion. The factors of physical fitness or training vary in different individuals and exaggerate the problem of defining mild heart failure on the basis of physiological tests or the development of symptoms such as breathlessness. Nevertheless, the response of the cardiac output to a standardized exercise test has been studied in patients with heart failure as well as in normal subjects.[69] These observations have shown that the cardiac output following exercise does not increase to a normal degree in patients with congestive heart failure. In mild cases of failure the cardiac output may be normal at rest and rise less than normally and presumably inadequately with exercise. This denotes some, although diminished, cardiac reserve. In very severe cases of heart failure the cardiac output is low and presumably inadequate even when the patient is at rest; with exercise there may be no increase whatever in the cardiac output, indicating no cardiac reserve—i.e., the cardiac output at rest [redacted] the maximal which the heart can deliver. But occasional cardiac patients with clinical evidence of heart failure may have a normal cardiac output at rest and an apparently normal increase with exercise even when they exhibit abnormal breathlessness during and after the exercise.[33] In such cases, however, the rise in cardiac output causes an abnormal rise in pulmonary capillary and arterial pressure.

In summary, the determinations of cardiac output in congestiv[redacted] heart failure generally confirm an association between the presence of heart failure and a diminished cardiac output. With some exceptions the correlation [redacted] quantitative in that the cardiac output is more regularly and more intensely diminished with more advanced heart failure. Furthermore, the ability of the heart to increase its output with exercise is depleted with increasing severity of the heart failure. However, in the light of the definition of heart failure in terms of inadequate cardiac output, one might anticipate a more consistent and a more marked reduction in cardiac output than one occasionally observes, particularly in the early and milder cases of heart failure. This deficiency in correlation may be due partly to technical difficulties in the determination of the cardiac output and partly to compensating homeostatic mechanisms that tend to maintain or restore the cardiac output as close to normal as possible.

Relation between Changes in Cardiac Output and Improvement of Symptoms. If heart failure is related to a deficiency in cardiac output, clinical improvement should correspond to an augmentation of the cardiac output. Harrison et al.[44] determined the cardiac output in 15 patients with congestive heart failure and again after the symptoms of heart failure had disappeared. With clinical improvement the cardiac output per minute increased in 3 cases and diminished in 7 cases, and the stroke output increased in 9, diminished in 3; there was no change in the remaining cases. On the other hand, Seymour et al.[103] found that the mean cardiac output during heart failure was 31 per cent less than after improvement; the output per minute and per stroke increased in every case when heart failure was controlled. More variable but consistent increases in cardiac output were reported by Eichna et al.,[29] McMichael and Sharpey Schafer[88] and Howarth and associates,[74] using the direct Fick method, observed striking increases in cardiac output in patients with low cardiac output and congestive heart failure when the patients were treated by digitalis, venesection and the application of tourniquets.

Reduced Cardiac Output without Symptoms of Congestive Heart Failure. Although the cardiac output is generally reduced in patients with congestive heart failure, it does not follow that the symptoms which characterize congestive heart failure are directly and specifically due to the deficient cardiac output, i.e., to an inadequate blood flow to individual tissues or organs. Thus in various states of shock or collapse due to trauma, hemorrhage or other causes the cardiac output is usually much lower than in cases of congestive heart failure, yet dyspnea, orthopnea, cardiac asthma, subcutaneous edema and other cardinal features of congestive heart failure are absent or insignificant. Conversely, the symptoms in shock which can be clearly related to a reduction in cardiac output, i.e., to an inadequacy of blood supply, such as weakness, mental torpor, fatigability, hypothermia, hypotension, are not observed or are overshadowed in cases of congestive heart failure.

Cardiac Failure with High Cardiac Output. There are groups of cases with unequivocal features of congestive heart failure in which

the cardiac output is actually increased This paradox is readily explained if one bears in mind that the physiologic definition of heart failure relates cardiac output to the needs of the tissues and not to some absolute normal Severe anemia, hyperthyroidism arteriovenous fistula beriberi advanced pulmonary emphysema with arterial hypoxemia pregnancy and occasionally advanced osteitis deformans are conditions which are or may be associated with an augmented cardiac output These abnormally high outputs are presumably necessary to supply increased tissue demands or to compensate for some factor interfering with an adequate supply of oxygen (p 186)

When cardiac failure develops as a complication of these conditions the cardiac output falls somewhat from the previously elevated levels but these reduced cardiac outputs are still distinctly above normal It is presumed however that these cardiac outputs although elevated are insufficient for body needs and therefore lead to the manifestations of heart failure If the heart failure is controlled e g by digitalis but the basic condition such as severe pulmonary emphysema remains the cardiac output is increased [illegible] If the basic condition responsible for the primary increase in cardiac output is controlled or cured the cardiac output falls to normal In a case of beriberi heart failure studied by Burwell and Dexter[5] the cardiac output was 11 8 liters and fell to a normal of 5 3 liters after clinical recovery

Cardiac Output Arterial Blood Pressure and Peripheral Resistance The systemic arterial blood pressure is not significantly altered during congestive heart failure except as it may be affected by the underlying cardiac disease or other factors Occasionally the blood pressure has been noted to be higher during severe heart failure (stauungshochdruck—Traube) than after recovery Since the peripheral systemic resistance (R) is proportional to the blood pressure (B P) and inversely proportional to the cardiac output (C O)

$$R = k\frac{B\ P}{C\ O}$$

An unchanged blood pressure with a diminished cardiac output indicates that the systemic resistance is increased in congestive heart failure (chiefly due to arteriolar vasoconstriction)

In cases of high-output heart failure the peripheral resistance is diminished not as a result of the heart failure but as a primary abnormality in the underlying disease e g hyperthyroidism or arteriovenous fistula The mean blood pressure may be normal slightly increased or slightly diminished, but the resistance is diminished to a greater degree hence the cardiac output is increased With the development of heart failure there may be a slight increase in the peripheral resistance which however, is still much below normal Therefore the cardiac output may fall somewhat, but is still more than normal

The blood pressure and peripheral resistance in the pulmonary circulation undergo changes which are often different and due to different mechanisms from those in the systemic circulation In left sided heart failure the pulmonary artery pressure and resistance are both usually increased at rest [illegible] but occasionally the pulmonary blood pressure is normal at rest[illegible] while the resistance is increased The increased resistance is located in the pulmonary capillaries and veins whereas the resistance in the pulmonary "arterioles" may or may not be increased in isolated left heart failure Exercise raises the pulmonary arterial blood pressure in heart failure, whether it is normal or elevated at rest [illegible] The pulmonary blood pressure rises with exercise but the cardiac output may or may not be augmented On the other hand the systemic blood pressure does not rise with exercise despite an increased cardiac output indicating that the systemic peripheral resistance diminishes with exercise in such cases

In right sided heart failure there is increased pulmonary blood pressure and increased pulmonary vascular resistance at rest Both increase further with exercise When the right heart failure is due to primary pulmonary disease the increased resistance is localized in the pulmonary arterioles When it is secondary to left sided heart failure the increased resistance is in the capillaries and veins as well as in the arterioles

Oxygen Utilization and Cardiac Output The provision of oxygen to the tissues after the blood becomes oxygenated is determined by the blood flow (cardiac output) and the amount of oxygen extracted per unit of blood (arteriovenous oxygen difference) Thus O_2 (Oxygen consumption) = C O (cardiac output) × (A_{O_2} − V_O) (arteriovenous oxygen difference) Normally an adult with a body

surface area of 1 6 sq meter may have a cardiac output of 5 liters per minute and an arteriovenous oxygen difference of 4 cc per 100 cc of blood (or 40 cc per liter) Such an individual consumes about 200 cc of oxygen per minute at rest (basal metabolism)

$$O_2 = \frac{5 \text{ liters}}{\text{min}} \times \frac{40 \text{ cc}}{\text{liter}} = \frac{200 \text{ cc}}{\text{min}}$$

During exercise oxygen needs increase and oxygen consumption can be readily increased 100 per cent or more In the normal individual this additional supply is provided chiefly by an increase in cardiac output, and to a lesser extent by increased extraction of oxygen from each unit of blood Thus for a required oxygen consumption during exercise of 400 cc instead of 200 cc per minute the cardiac output may be increased to 8 liters and the oxygen extraction per liter of blood (arteriovenous oxygen difference) to 50 cc per liter

$$O_2 \text{ (cc /min)} = \frac{8 \text{ l}}{\text{min}} \times \frac{50 \text{ cc}}{\text{l}} = \frac{400 \text{ cc}}{\text{min}}$$

In congestive heart failure the oxygen consumption at rest (basal metabolism) is somewhat increased possibly owing to increased work of the muscles of respiration Thus instead of an oxygen consumption of 200 cc per minute as in the above theoretical example, it might be 240 cc Since the cardiac output is *diminished in heart failure, the needed oxygen* supply is obtained by an abnormally large oxygen extraction per unit of blood Thus if the cardiac output is 3 liters instead of the normal 4 liters in the above example the arteriovenous oxygen difference (extraction) is 80 cc per liter instead of 40 cc

$$O_2 = \frac{3 \text{ l}}{\text{min}} \times \frac{80 \text{ cc}}{\text{l}} = \frac{240 \text{ cc}}{\text{min}}$$

Since the arterial oxygen is usually normal in heart failure (190 cc per liter) the mixed venous oxygen would be only 110 cc per liter During exercise the patient with heart failure can increase his output less than normally or not at all Similarly he may not be able to increase his oxygen consumption and an increased oxygen debt is sustained When oxygen consumption is increased during exercise in a patient with congestive heart failure, most or all of the increase is effected by greater oxygen *extraction per unit of blood* rather than by increased blood flow (cardiac output)

Increased oxygen consumption is an index of increased bodily requirement When cardiac function is normal, an augmented cardiac output supplies most and increased oxygen extraction some, of the increased oxygen need When the heart fails the cardiac output no longer contributes its share to increased bodily requirement for oxygen and the elevated oxygen consumption must be supplied in increasing degree by greater oxygen extraction When heart failure is mild oxygen extraction per unit of blood may be normal at rest and increased abnormally with exercise In severe heart failure, oxygen extraction is excessive at rest and more so with exercise In very severe heart failure maximal oxygen supply is effected at rest for a given low cardiac output by maximal oxygen extraction Neither oxygen consumption cardiac output nor oxygen extraction can be increased with exercise

It is apparent that increasing severity of congestive heart failure is indicated by progressively increased oxygen extraction Since arterial oxygen usually remains relatively normal, there is a progressive diminution in *mixed venous oxygen as the cardiac output* fails to supply oxygen requirements

In diseases with high cardiac output such as arteriovenous fistula, severe anemia, etc (but not hyperthyroidism) the oxygen consumption is normal despite the augmented blood flow Thus the oxygen extraction per unit blood is low i e 25 cc per liter instead of 40 to 50 cc, and the mixed venous oxygen is 165 cc instead of 150 to 140 cc For example if the oxygen consumption (O_2) is normal at about 200 cc per minute and the cardiac output elevated to 8 liters per minute, the oxygen extraction (arterial oxygen (190 *cc per liter) — venous oxygen (165 cc per* liter)) would be 25 cc per liter

$$O_2 = \frac{8 \text{ liters}}{\text{minute}} \times \frac{25 \text{ cc}}{\text{liter}} = \frac{200 \text{ cc}}{\text{minute}}$$

When the heart fails, the cardiac output falls somewhat from this high level and the oxygen consumption (which remains normal or elevated at rest) is effected by an increased oxygen extraction However just as the cardiac output, though diminished, may remain above normal levels the oxygen extraction though increased as in low output failure may remain below normal levels

In the above example the high cardiac output may fall in heart failure from 8 liters to 6 5 liters the oxygen consumption may remain 200 cc per minute, and the oxygen extraction would rise to 31 cc instead of 25 cc

but would still be less than the normal of 10 to 50 cc per liter

$$O_2 = \frac{6.5 \text{ liters}}{\text{minute}} \times \frac{31 \text{ cc}}{\text{liter}} = \frac{200 \text{ cc}}{\text{minute}}$$

Pulmonary Ventilation and Oxygen Consumption in Heart Failure

Pulmonary ventilation in heart failure is discussed on page 147 It is mentioned here to call attention to the limitations which congested lungs in heart failure may impose in supplying oxygen to the blood and thence to the tissues As a rule the blood is adequately oxygenated at the expense of increased ventilation per unit of time accomplished by increased respiratory effort and work of the respiratory muscles

The Intracardiac Pressures

When the work of the right ventricle is increased by a pathologic lesion such as pulmonic stenosis the cardiac output may be maintained at normal levels by compensatory hypertrophy The right ventricular systolic pressure is elevated to various heights above 30 mm Hg the upper limit of normal and may even equal or exceed left ventricular pressure On the other hand the end diastolic pressure remains normal at 5 mm Hg or less as long as compensation is complete With the development of heart failure the ventricular end diastolic pressure rises to 10 to 20 mm Hg or higher The right atrial pressure also rises its pressure being approximately equal to the elevated end diastolic pressure of the ventricle[17, 66] Similar elevations of the right ventricular end diastolic pressure and right atrial pressure occur in right ventricular failure due to a variety of other causes including preceding left heart failure

Similarly when the left ventricle fails the left ventricular end diastolic pressure rises[162] and subsequently the left atrial pressure rises to the same degree When failure of the left side of the heart is due to mitral stenosis left ventricular end diastolic pressure is normal but the pressure in the left atrium the failing chamber is quite elevated

Venous Pressure The elevated right atrial pressure in right-sided heart failure is reflected in a corresponding rise in pressure in the venae cavae the smaller systemic veins and presumably in the systemic capillaries The venous pressure in the antecubital vein normally between 4 and 10 cm water (3 to 8 mm Hg) usually measures 10 to 20 cm but occasionally is as high as 30 cm water or more In milder cases of right heart failure the systemic venous pressure may be normal at rest but elevated with exercise

In isolated failure of the left side of the heart the systemic venous pressure is normal However, the elevated left atrial pressure is reflected in a corresponding increase in pressure in the pulmonary veins and pulmonary capillaries

The rise in venous pressure denotes an inability of the failing chamber to accept and eject the venous return as competently as the normal chamber The venous pressure is thus the resultant of these two factors venous return and cardiac accommodation to changes in venous return This may also be expressed in terms of the formula Pressure = blood flow (venous return) × resistance In heart failure the blood flow or venous return is usually diminished for the venous return equals the cardiac output Since the venous pressure is elevated whereas the blood flow is diminished the resistance must be increased to a greater extent than the blood flow is diminished The increased resistance is apparently due to the resistance offered by the failing chamber with its high residual volume and high end diastolic pressure

Factors which increase the venous return such as shifting from the upright to the recumbent position exercise infusions and transfusions do not raise the venous pressure in the normal individual since the increased venous return is readily accepted by the heart and translated into an increased cardiac output In heart failure an increased venous return cannot be properly accepted and ejected by the failing chamber This leads to further stasis and increased pressure in the failing chamber and in the veins proximal to it[69, 134] On the other hand changing from the recumbent to the upright position venesection[74] and mercurial diuresis[10] which tend to reduce the venous return depress the elevated venous pressure in heart failure

It is claimed that heart failure is associated with increased venomotor tone (diminished venous distensibility)[161] just as there is increased vasomotor tone of the arterioles The increased venous pressure in heart failure has been attributed to this heightened venous tone[22] However, increased venous tone per se could not account for such pressure change Thus in cases of shock due to hemorrhage

there is marked increase in venous tone but a fall in venous pressure The fall is due to a decrease in venous return without an increase in cardiac resistance to inflow On the other hand the venous pressure may be normal in mild right sided heart failure despite increased venomotor tone Nevertheless simple *leg exercise raises the venous pressure not* because of a rise in venous tone but because the increased venous return due to exercise cannot be handled by the failing right heart

The Circulating Blood Volume

That the circulating blood volume is increased in congestive heart failure has long been indicated clinically by the presence of intense venous engorgement (high venous pressure distention of superficial veins hepatic enlargement and pulmonary engorgement) without a corresponding depletion of the arterial system The absence of substantial arterial depletion is indicated by the maintenance of arterial blood pressure and absence of cold extremities or other phenomena of shock An increase of circulating blood volume in cases of congestive heart failure is also indicated by the observation at necropsy of dilated blood filled cardiac chambers and by the intense engorgement of the blood vessels and viscera including the lungs liver and gastrointestinal tract According to Nylin[112] *most of the increased blood volume is* in the cardiac chambers (See also Heimbecker et al [67])

Actual determinations of the circulating blood volume while in some disagreement mostly reveal a definite increase in patients with congestive heart failure (infra) Hamilton *and his co-workers*[61] *demonstrated* an augmentation of the intrathoracic blood volume the volume of blood in both the heart and in the lungs being increased during congestive heart failure but not in patients with compensated heart disease Gibson and Evans[56] found the total blood volume definitely increased during congestive heart failure but especially in patients whose venous pressure exceeded 10 cm of water and whose circulation time was prolonged When the venous pressure was above 15 cm of water the average increase in the circulating blood volume was roughly parallel to the prolongation in circulation time and the elevation of the venous pressure With the subsidence of symptoms the blood volume fell the diminution being greatest in those patients with the greatest clinical improvement In most patients the blood volume decreased a liter or more and occasionally there was a reduction of 3 5 liters

Wollheim[160] also found in extensive studies of the circulating blood volume that this was increased in most patients with cardiac failure A study of his cases reveals that the patients with an increased blood volume were suffering from congestive heart failure termed by Wollheim[160] plus decompensation Of the patients with a diminished blood volume (40 to 60 cc per kilogram) the so called group of minus decompensation, many included instances of shock with or without congestive heart failure Insufficient clinical data are provided in Wollheim's publication to permit an interpretation of his cases and findings

While studies using the dye dilution method and some of those using radioactive iron have fairly uniformly disclosed an increase in plasma volume in heart failure,[66 6 133 99] some of the recent measurements of red cell volume by tagging erythrocytes with P^{32},[1 118 126] indicated that there is little or inconstant increase in red cell volume or in plasma or total blood volume in most patients with congestive heart failure These are in some disagreement with the determinations of Nylin [112] who used erythrocytes tagged *with* P^{32} *or thorium B and found uniform in*creases in red blood cell volumes which became more prominent with increased severity and especially with increased duration of the congestive heart failure More recently Reilly and associates using radiochromium Cr^{51} found an increased blood volume in the majority of patients with right heart failure but not in those with left ventricular failure or in mitral stenosis alone [1] findings similar to those of Nylin and Hedlund [113] Brown et al found that the whole blood volume and *the volume of red blood cells determined by* carbon monoxide and radiochromium Cr^{51} usually increased in congestive heart failure and decreased with improvement and similar findings were reported by Gunton and Paul who used P^{32} tagged erythrocytes Eisenberg [40] using the radio-chromium method found an increase of 20 per cent in blood volume (23% in cell mass, 17% in plasma volume) in congestive heart failure In mild case there was a 14 per cent increase in severe cases a 38 per cent increase in blood volume Increased blood volume was correlated with

the degree of cardiac enlargement, following treatment reduction in blood volume occurred and paralleled diminution in cardiac size

The reason for the discrepancy between blood volumes in heart failure determined by the dye method and those determined by tagging red blood cells may be clarified by a consideration of the total body hematocrit relative to that determined from venous blood as is usually done The hematocrit determined from blood drawn from a large vein is higher than the over all body hematocrit (red cell volume relative to total blood volume)[35, 8, 73] Thus plasma volumes and total blood volumes determined from red cell volumes and venous hematocrit are both underestimated Recently Schreiber and associates[1, 9] made simultaneous determinations of the red cell volume with P^{32} and of the plasma volume by means of I^{131} labeled human serum albumin in control subjects and in patients with congestive heart failure They found that the mean values for red blood cell volumes and plasma volumes in heart failure were elevated above those in control subjects and fell with compensation Furthermore during heart failure the hematocrit determined from venous blood relative to the total body hematocrit was even greater than normal thus tending to further underestimate plasma volume and total blood volume as calculated from red cell volume and venous hematocrit This may account for some of the relatively slight increases in blood volume or normal blood volumes reported in congestive heart failure, when the blood volume was determined from the red cell volume and hematocrit

The increase in plasma and total blood volume in heart failure is relatively small in comparison with the vast increase in extracellular fluid (plasma plus interstitial fluid) observed in patients with heart failure especially those with severe edema and effusions in the serous cavities Plasma volume is often increased 10 to 20 per cent in moderately severe cases of heart failure 30 to 50 per cent in very severe cases On the other hand the extracellular fluid chiefly interstitial fluid may be increased 100 per cent or more

The Circulation Time (p 213)

As a rule the circulation time (arm vein to tongue) in cases of congestive heart failure varies between 20 and 40 seconds instead of the normal of 10 to 16 seconds but occasionally it is 50 seconds or more Most of the circulatory slowing occurs in the pulmonary vessels and/or in the enlarged cardiac chambers[35, 108, 18, 112] The circulation time (arm to-tongue) may be prolonged in pure right sided heart failure due to delay in passage of the test substance from the arm vein to the lungs the lung to-tongue time (p 215) may be normal In pure left sided heart failure the arm to tongue time may be prolonged because of delay in circulation from the lung to the tongue while the arm to-lung time is normal The increase in circulation time or reduced speed of blood flow occurs in areas where there is a widening of the stream i e in the distended veins and the decompensated cardiac chambers without corresponding increase in quantity of blood flow But one must regard the reduced speed of blood flow as primarily due to a diminished driving force represented by the diminished cardiac output

The venous return to the heart is proportional to the circulating blood volume and to the speed with which this flows or inversely proportional to the circulation time Since the cardiac output is diminished in heart failure and the venous return is equal to the cardiac output the venous return is likewise diminished The increased circulating blood volume usually observed in heart failure would tend to augment the venous return if its speed of flow were unaltered However the fact that the venous return is reduced despite increased circulating blood volume denotes that slowing of the blood stream (increased circulating time) is more marked than increase in blood volume

In diseases associated with high cardiac output (arteriovenous fistula hyperthyroidism severe anemia et al) as well as during marked fever or exercise the circulation time is diminished or the speed of flow is increased[63] The venous return to the heart is augmented because of the increased speed of flow which outweighs any changes in circulating blood volume Accordingly the cardiac output is also enhanced With the occurrence of heart failure in the above diseases, the speed of the circulation falls but the circulation time may still be normal or slightly diminished Furthermore the circulating blood volume increases Hence the venous return (and likewise the cardiac output) is still

greater than normal since the blood volume is above normal and its speed of circulation normal.

FLUID AND ELECTROLYTES IN CONGESTIVE HEART FAILURE (see p. 275)

Fluid Retention and Abnormal Distribution

Excessive retention and abnormal distribution of fluids are striking features of congestive heart failure and appear to account for the major clinical manifestations. Almost identical clinical manifestations may occur in non-cardiac subjects who experience marked water retention following administration of steroid hormones, although there is no evidence of failure of the heart as a pump.[4] Although water diffuses freely through the membranes separating the blood vessels and cells from intercellular fluid, the total body water may be regarded as more or less quantitatively segregated into compartments, the intracellular and extracellular, and the latter further subdivided into the vascular and interstitial compartments. The relative integrity of these compartments is preserved by the membranes lining the blood vessels and cells—the vascular membrane by virtue of its relative impermeability to serum proteins and the cell membranes by similar impermeability to cell protein and by selective permeability to various electrolytes. The abnormal fluid retention that occurs in heart failure affects not only different body areas but also different fluid compartments in varying degree.

Although there are technical difficulties in the determination of total plasma, extracellular and intracellular water (see Chap. 10) and although these are magnified in heart failure because of the delay and uncertainty in obtaining uniform mixing of the injected test substance, reasonable approximations have been obtained.

Table 2 shows the distribution of body water in normal persons and in congestive heart failure for a body weight of 60 kg. Intracellular water, probably increased in heart failure, is assumed to be unchanged.

Table 2

	NORMAL		HEART FAILURE	
Compartment	Per cent body wt	Liters (Wt 60 kg)	Per cent body wt	Liters (Wt 70 kg)
Plasma	4.5	2.7	5.4	3.8
Interstitial	11.5	6.9	22.6	15.8
Extracellular	16.0	9.6	28.0	19.6
Intracellular	40.0	24.0	34.3	24.0
Total Body Water	56 [illegible]	33 [illegible]	62.3	43.6

Even without such determinations it is apparent that in advanced congestive heart failure vast quantities of water are retained in the extravascular extracellular fluid as revealed clinically by massive edema and large effusions in the serous cavities of the body. Various determinations of plasma volume have generally indicated a moderate increase of 10 to 50 per cent. Since the normal plasma volume in the adult is often only 2.5 to 3 liters, such increases as occur in heart failure, ranging from 0.5 to 1.5 liters, account for only a small part of the fluid retained. On the other hand, the remaining interstitial portion of the extracellular fluid (i.e., outside the blood vessels and outside cells) is commonly doubled or trebled in quantity and amounts in absolute terms to 15 or 20 liters instead of a normal of about 7 liters for an adult weighing 60 kg.

Changes in total body water may be estimated when there is a rapid weight gain in a patient developing congestive failure or more often when there is a rapid weight loss as a patient with heart failure is reduced to virtually dry weight by effective treatment. The increase in total body water is due essentially to increased extracellular water. Intracellular water, calculated by subtracting extracellular from total body water, cannot be determined with adequate accuracy in congestive heart failure. Direct determination of intracellular water on tissue biopsies of *skeletal muscle suggests that water is retained* within the intracellular as well as in other compartments.[106] Certain electrolyte and water balance studies made during recovery from heart failure[137, 103, 94, 1] also suggest that there is an increase in intracellular as well as extracellular water in congestive heart failure. *Water excretion during recovery from heart* failure has been found to be in excess relative to sodium, i.e., in comparison with the sodium concentration in serum, suggesting that water comes out of the cells during recovery from heart failure.[94, 103]

The changes in water distribution in the

various compartments in advanced congestive heart failure is indicated in Table 2. Perhaps the most striking finding is that the increase in interstitial fluid (edema) far exceeds the total plasma water. Therefore one cannot account for the edema by transudation from the blood stream due to elevated venocapillary pressure unless concomitantly there is some other mechanism for retention of water to replace the vast quantities lost from the blood stream to interstitial tissue.

In patients with right sided heart failure water retention is best observed in the lower extremities presumably owing to gravity and its hydrostatic effect in increasing capillary pressure. When the patient is recumbent edema of the lower extremities disappears or is alleviated and may then appear in the sacral region which is now the lowest part of the body. In patients with isolated left sided failure water retention is often not prominent and may *be difficult to demonstrate*. Nevertheless there is usually a delay beyond normal in excreting a water load.[80] Determinations of residual blood volume[112] and intrathoracic blood volume[54, 84] (p. 223) indicate that the increase in circulating blood volume is localized in large measure to the dilated, failing cardiac chambers and probably in the pulmonary circulation.

Sodium Retention in Heart Failure

It appears to be established that the abnormal retention of fluid in congestive heart failure is secondary to the abnormal retention of sodium ion. The integrity of the living cell is dependent on a constant osmotic pressure of the surrounding extracellular fluid which the body guards by various homeostatic mechanisms. The concentration of sodium ion in extracellular fluid is responsible for almost all the osmotic pressure due to cations and its constancy may be regarded as a measure of the constancy of the osmotic pressure. When the concentration of sodium in the blood increases the posterior pituitary gland is stimulated to secrete antidiuretic hormone, water is retained by the kidney and the normal concentration of sodium and the normal osmotic pressure is restored.[149, 114] This is the general manner in which it is assumed that the primary abnormal retention of sodium leads also to abnormal retention of water in congestive heart failure. But other mechanisms also are probably concerned in the regulation of water balance in congestive heart failure, for water may be retained even when the sodium concentration is below normal and the extracellular fluid is hypotonic.

That sodium and not water retention is the primary defect in heart failure is indicated by the common clinical experience that even a moderate intake of sodium by patients with heart failure increases clinical symptoms and results in rapid weight gain and edema due to fluid retention. On the other hand the intake of large quantities of water, except under unusual circumstances, does not increase edema and may even promote diuresis[1, 7] provided sodium intake is minimal. The rapid infusion of sodium-containing fluids or the oral ingestion of large amounts of sodium by patients with heart disease is frequently followed by the clinical picture of heart failure.[83, 119, 1, 2, 152] Conversely, striking relief of the symptoms and signs of heart failure has been effected by *maintaining an extremely low sodium intake*.[130]

The abnormal retention of sodium is also indicated by the inability of patients in heart failure to excrete a sodium load as do normal subjects. Futcher and Schroeder[53] injected 400 cc. of 6 per cent sodium chloride solution intravenously over a period of thirty minutes in patients convalescing from congestive heart failure. The renal excretion of sodium and chloride in the next twenty four hours was not more than 30 per cent of that observed in normal controls. Similarly Proger et al.[119] administered excessive amounts of sodium chloride by mouth to patients recently recovered from heart failure and observed an abnormal retention of sodium concomitant with the occurrence of their symptoms. That it is the sodium ion and not the chloride of sodium chloride which is responsible is indicated by the observation that the administration of other sodium salts is similarly associated with abnormal sodium and water retention, whereas chloride ion in the form of ammonium chloride does not cause a retention of salt or water and in fact produces a diuresis. Tracer studies with radiosodium (Na^{24} and Na^{22}) have shown an increase in total body sodium[1] as well as delayed excretion and retarded turnover of sodium during heart failure.[25, 146] The total body sodium is increased to 56.7 milliequivalents per kilogram of body weight instead of the normal

value of 35 2 milliequivalents per kilogram[150] The abnormal response of a patient in heart failure to a sodium load is indicated in the accompanying table

Table 3 Urinary Output of Sodium

After 500 cc of 5% sodium chloride (428 mEq) intravenously in 30 minutes in normal control and in patient with heart failure

INTERVALS AFTER IV Minutes	CONTROL Na Excreted mEq	% of load	HEART FAILURE Na Excreted mEq	% of load
140	101	23 6	12 4	2 9
310	51	11 9	10 3	2 4
750	105	24 5	12 5	2 9
Tot 1200 (20 hours)	257	60 0	35 2	8 2

Electrolyte Concentrations in Extracellular and Intracellular Fluid

The normal concentrations of the major extracellular and intracellular electrolytes are shown in Table 4

Table 4 Electrolyte Concentrations

	PLASMA[44] mEq /lit.	INTERSTITIAL FLUID mEq /lit	INTRACELLULAR mEq /liter cell water
Sodium	142	140	14[44]–37[28]
Potassium	4 5	4 5	106–112[3, 28]
Chloride	103	106	25[28]
Bicarbonate	27	28	10 (?)

Considerable uncertainty still exists as to the intracellular concentrations in normal individuals in heart failure this uncertainty is magnified due to technical difficulties especially the delay in obtaining complete homogeneous mixing of the injected test substance Determination of intracellular sodium and potassium concentrations is further complicated by the presence of large stores of these cations in bone[13] approximately 30 per cent of the body sodium has been estimated to be contained in bone and about 45 per cent of this is exchangeable[18] Dilution studies with radioisotopes have indicated that the intracellular concentrations of sodium and chloride are considerably greater than was previously thought and therefore that the cell membrane was not as impermeable to these ions as had been believed[88, 4, 3]

The concentration of electrolytes in the plasma and interstitial fluid in heart failure is usually relatively normal or only slightly altered Treatment with low sodium diets and mercurial diuretics is instituted so commonly before patients are hospitalized and their electrolytes studied that it is difficult to be certain whether or to what extent altered plasma electrolyte patterns are the result of heart failure or of the treatment Slight to moderate reductions in plasma sodium concentration are common possibly due to low sodium intake High plasma sodium concentration which might be expected on the basis of the abnormal sodium retention has been *reported*[118, 137, 77] *but is rare Despite low* sodium concentration *total body sodium* is quite elevated in heart failure[118, 150] since an approximate reduction of 7 per cent in plasma *sodium concentration* (e g from normal of 140 to 130 milliequivalents per liter in heart failure) is more than outweighed by an increase of 100 to 200 per cent in the extracellular fluid volume (plasma and interstitial fluid) containing this concentration of sodium Other changes in electrolyte pattern in heart failure due to mercurial diuretics other drug or renal or pulmonary complications are discussed in Chapter 11

Intracellular electrolyte changes in congestive heart failure have been reported on the basis of direct analysis of cardiac and skeletal muscle post mortem[7, 45] and of biopsy specimens of skeletal muscle in vivo[106, 115] on the basis of balance studies during recovery from heart *failure*[74, 103, 137, 81] *and during mercurial diuresis*[47, 137] and by isotope dilution techniques[131, 4] Although the findings are not uniform in general these varied studies indicate that in congestive heart failure there is an increase in intracellular water and sodium and a diminution in intracellular potassium In cases of heart failure due to cor pulmonale there may be a cellular loss of water and sodium as well as of potassium[95] Determination of intracellular water and electrolytes by tissue analysis is especially difficult in the presence of tissue edema in heart failure Reduction in electrolyte concentration may also be due to dilution by tissue edema rather than to absolute reductions Striking transfers of sodium potassium and water between the extracellular

and intracellular compartments appear to occur during the development of and during the recovery from congestive heart failure Iu k and Palmer[94] observed that when a patient who had recovered from heart failure was given fairly large quantities of sodium expansion of the extracellular fluid space and clinically manifest heart failure did not occur until after the intracellular space was saturated with sodium The realization that cells are more readily permeable to sodium and chloride than was previously recognized and that a considerable percentage of bone sodium is readily exchangeable may invalidate some of the earlier calculations in balance studies

It is obvious that a greater knowledge of the intracellular electrolytes and their behavior in congestive heart failure would be valuable in understanding the sequence of events leading to the clinical picture of congestive heart failure The renal retention of sodium and water may be initiated by intracellular water and electrolyte disturbances caused when the cardiac output becomes deficient and interferes with normal cellular metabolic processes Since recent studies with radioisotopes have shown a rapid exchange of sodium ions across cell membranes and a higher cellular concentration of sodium than was previously thought our concept of cell membrane impermeability to sodium has undergone revision According to one theory [70] [8] sodium ions enter the cell readily but a mechanism of carrier molecules acts as a ' pump to extrude from the cell most of the sodium that diffuses into it The energy for such work is conceived as being supplied by intracellular reduction and oxidation reactions The energy is transferred to carrier enzymes which combine with sodium ion and carry it to the cell membrane for extrusion out of the cell Balancing of sodium outflow by potassium inflow maintains both electrical neutrality and normal intracellular osmolarity

It is of interest that the retention of water and sodium and loss of potassium by the cells in heart failure are similar to the increased sodium and water content and loss of potassium by skeletal muscles during contraction and to the release of cellular potassium and increase in sodium associated with membrane depolarization by a nerve impulse It may be speculated whether cardiac failure with its deficient blood flow disturbs the mechanism of energy production or energy transfer in cells, thereby impairing the pump mechanism for intracellular electrolyte balance Such disturbance whether localized in all cells or predominantly in renal tubule cells could be concerned with the abnormal renal retention of sodium and water in congestive heart failure

Mechanism of the Abnormal Renal Retention of Sodium in Heart Failure

Not only is there uncertainty as to the intermediate steps between cardiac failure and the abnormal retention of sodium and water by the kidney but there is also disagreement as to the renal mechanism responsible for the sodium water retention Three mechanisms have been considered (1) elevation of renal venous pressure due to congestive heart failure, (2) diminution in glomerular filtration of sodium and water possibly due to reduced renal arterial blood flow (3) increased tubular reabsorption of sodium and water due to chemical hormonal or other influences

1 **Elevated Renal Venous Pressure** Sodium water retention by the kidney has been attributed to an elevated renal venous pressure and passive congestion of the kidney [88] An elevated venous pressure has been found by catheterization of the renal vein of patients with heart failure[94] these patients also had an elevated right atrial pressure denoting right sided heart failure Partial occlusion of one renal vein in dogs caused a diminution in sodium and water excretion only from the kidney subjected to an increased renal venous pressure (above 150 mm saline) [158] The disturbances in sodium water excretion appeared without distinct relation to changes in renal blood flow or glomerular filtration

In the experimental production of chronic pericarditis with effusion a reduction in renal output of water and sodium is associated with a rise in venous pressure even though resting cardiac output renal blood flow and glomerular filtration are at control levels [45] These acute experimental observations appear to support the theory that heightened renal venous pressure in heart failure impairs the renal excretion of sodium and water On the other hand more prolonged experimental elevation of renal venous pressure by partial ligation of the inferior vena cava in trained unanesthetized dogs disclosed an initial diminution in sodium excretion glomerular filtration and renal plasma flow but after a week

these had returned or were returning to normal even though the venous pressure was still elevated[75] Although prolonged inferior vena caval ligation *below* the diaphragm but including the renal vein was not followed by sustained retention of sodium and water prolonged experimental constriction of the inferior vena cava *above* the diaphragm, which caused congestion of the liver as well as of other abdominal viscera, led to sustained edema and ascites[1 3] Furthermore, by use of an intracardiac catheter with inflatable balloon it has been demonstrated in humans that not only elevation of renal venous pressure but also obstruction and venous congestion of the superior vena cava or of the inferior vena cava below as well as above the renal veins diminished the renal excretion of sodium and water[43]

It is questionable whether these experimental observations which do not duplicate the findings in chronic congestive heart failure in humans apply to the mechanism underlying the abnormal retention of sodium and water in heart failure But even if elevated renal venous pressure does diminish the excretion of sodium and water, it could not represent the initial cause for the renal impairment in heart failure because sodium and water retention occur in left sided heart failure before there is any elevation in systemic or renal venous pressure It is possible that elevated systemic or renal venous pressure may intensify the renal disturbance later in the course of heart failure when the right ventricle becomes insufficient and the systemic venous pressure rises

Table 5 Renal Hemodynamics in Congestive Heart Failure (After Heller and Jacobson[81])

	NORMAL	HEART FAILURE
Glomerular filtration rate cc /min	103	75 (54–105)
Renal plasma flow cc /min	603	190 (19–313)
Filtration fraction	0 174	0 323

2 Diminished Glomerular Filtration The studies of Merrill[100] and of Mokotoff, Ross and Leiter[105] and others[83] disclosed a reduction in renal blood flow and in the excretion of sodium and water in patients with congestive heart failure Renal blood flow was diminished more than cardiac output, indicating renal vasoconstriction Renal plasma flow was reduced more than glomerular filtration resulting in an increased filtration fraction, presumably due to constriction of the glomerular efferent arterioles Mokotoff et al[105] concluded that the retention of sodium was due to diminished glomerular filtration consequent to the diminished renal blood flow, and not to increased tubular reabsorption Tubular reabsorption was found to represent a constant percentage of the glomerular filtrate

But it should be recalled that great variations in the glomerular filtration of sodium and water are easily neutralized by small deviations in tubular reabsorption Normally about 99 5 per cent of the sodium and water in the glomerular filtrate is reabsorbed by the tubules A reduction of 50 per cent in glomerular filtration could be neutralized and a normal sodium excretion effected if the tubular reabsorption diminished merely from 99 5 to 99 0 per cent To attribute the impaired sodium excretion to reduced glomerular filtration alone it is necessary to prove that tubular reabsorption is absolutely unchanged But in one of the patients studied by Merrill[100] 99 99 per cent of the sodium filtered by the glomeruli was reabsorbed and in another 99 96 per cent instead of the normal 99 5 per cent Similarly the figures of Mokotoff et al[105] strongly suggest that tubular reabsorption is increased despite their conclusions to the contrary I have observed instances in which no sodium was excreted during whole days in patients with congestive heart failure[81] Significant variations in tubular reabsorption, sufficient to cause considerable retention of sodium are of such small magnitude that they could easily be obscured by the range of error of the methods now available

Other objections have been raised to the belief that renal impairment of sodium and water excretion is due entirely or primarily to *diminished glomerular filtration* Glomerular filtration is diminished in essential hypertension but there is no significant renal retention of sodium and water Edema does not occur in many cases of intrinsic renal disease in which glomerular filtration is substantially reduced This has suggested that a glomerulo-tubular imbalance rather than defective glomerular filtration alone causes sodium water retention and edema In occasional cases of congestive

heart failure an impairment of renal excretion of sodium and water is observed although glomerular filtration is normal[135] Patients in heart failure have been observed to regain clinical compensation without a significant augmentation of their glomerular filtration rate[133 1 135 21] although the ability to excrete sodium was restored

It appears that reduction in glomerular filtration of the degree commonly observed in congestive heart failure results in a significant diminution in sodium excretion, provided tubular reabsorption remains normal or increases But it is improbable that this is the sole or essential factor in the abnormal retention of sodium and water by the kidney in congestive heart failure

3 **Increased Tubular Reabsorption** . Abnormal renal excretion of sodium in heart failure may be due to increased tubular reabsorption[44 135] This is suggested by our knowledge that the tubules are important in the regulation of sodium metabolism especially in maintaining the pH the isotonicity and the volume of body fluids Tracer studies with radioisotopes of sodium led Burch Reaser and Cronvich[-] to conclude that diminished sodium excretion was due to an increased percentage of reabsorption of this electrolyte from the glomerular filtrate The instances in which I have observed no excretion of sodium at all for twenty four hour periods also support this conclusion The ability of many patients to maintain sodium balance despite impaired glomerular filtration indicates that the percentage of tubular reabsorption of sodium can be regulated independently of filtration[59] On the other hand it has been postulated that there is a threshold or limited transfer mechanism for sodium reabsorption in the distal tubule Thus with increased sodium filtration the distal tubular reabsorptive capacity may be exceeded and more sodium is excreted with diminished glomerular filtration the small load reaching the distal tubule may be virtually entirely reabsorbed According to this view increased tubular reabsorption is determined by impaired glomerular filtration

Indirect evidence of the importance of exaggerated tubular reabsorption of sodium rather than diminished glomerular filtration in heart failure is provided by studies of renal hemodynamics during and after exercise Kattus Sinclair Smith and associates[8] found that exercise produced sodium retention in normal individuals without alteration of filtration rate and in patients with congestive heart failure exercise produced sodium retention with or without reduction in glomerular filtration Furthermore, when filtration was diminished it returned to normal after cessation of exercise while sodium retention was still present

Experimental studies with sodium loading also suggest that diminished sodium excretion in heart failure is due to increased tubular reabsorption Barger Rudolph and Yates[7] measured renal clearances following intravenous infusions of sodium chloride in dogs with mild heart failure due to experimentally produced valvular lesions While renal plasma flow and glomerular filtration rose to a normal degree after the infusion sodium and water excretion were decreased as a result of more complete tubular reabsorption

Mechanisms Increasing Tubular Reabsorption of Sodium

Excessive tubular reabsorption of sodium and water in heart failure may be mediated through the secretions of endocrine organs, notably the anterior pituitary or adrenal cortex, through other humoral agents or by local changes in tubular cellular metabolism

Adrenal Cortical Hormones The adrenal cortex has been assigned a primary role in the regulation of sodium and water chiefly by endocrine regulation of tubular reabsorption of sodium The adrenal cortical hormones desoxycorticosterone and aldosterone are powerful sodium retaining factors To a much lesser extent ACTH cortisone and hydrocortone cause an early renal retention of sodium despite the fact that there is a rise in glomerular filtration Unless sodium intake is sharply restricted their administration may cause edema pulmonary edema, and in fact many of the hemodynamic disturbances usually associated with congestive heart failure[8] Similarly desoxycorticosterone, which probably acts on the tubules is capable of inducing heart failure when given in excess to patients with Addison s disease These similarities have suggested that the secretion of adrenal corticoid hormones may actually represent an intermediate mechanism in heart failure whereby the renal tubules are influenced to abnormal retention of sodium and water and the production of the clinical features found in heart failure

There is considerable evidence that various

stresses or threats to bodily homeostasis evoke reactions by way of the adrenal cortex Failure of the heart may represent such a stress with a corresponding adrenal cortical response An increased amount of urinary corticoids[115] and the sodium retaining corticoid, aldosterone[93, 5] have been found in the urine of patients with congestive heart failure[138] The reduction of sodium output in the sweat[100] saliva[15] and feces[12] as well as in the urine of patients with heart failure suggests that abnormal sodium retention in heart failure is not a local renal effect but rather the consequence of adrenal cortical action on multiple sites including the renal tubules The exact stimulus to the hypothesized excessive adrenal cortical activity is unknown Since impairment of liver function is common in chronic congestive heart failure it has been suggested that the liver is deficient in its inactivation of adrenal corticoids But this mechanism would not apply to isolated left heart failure

Antidiuretic and Other Hormones The renal retention of water rather than sodium per se causes many of the outstanding features of heart failure but the water retention is regarded as secondary to retention of sodium The latter in turn stimulates the hypothalamic posterior pituitary axis to secrete antidiuretic hormone (ADH) which acts on the distal tubule to inhibit the excretion of water without directly affecting that of sodium The water retaining effect of ADH results in a more concentrated urine of diminished volume but the absolute quantity of sodium in the urine is unchanged[7] Therefore ADH is *not regarded as a primary factor in the accumulation of excessive fluid in congestive heart failure*

Bercu and associates[10] found an antidiuretic substance in the urine of 12 of 15 patients with cardiac edema Similar antidiuretic substances have been discovered in the urine of patients with cirrhosis of the liver toxemia of pregnancy and Cushing's disease But the finding of antidiuretic pitressin like substances in the urine in states associated with abnormal sodium water retention such as cirrhosis of the liver and congestive heart failure may be interpreted as the secondary consequence of disturbances in fluid and electrolytes in these conditions rather than as the initiating factor Since the liver normally inactivates ADH the accumulation of antidiuretic substances may be the result of liver dysfunction in cirrhosis and in heart failure[15] But recent studies have indicated that ADH is normally inactivated in patients with cirrhosis of the liver[14, 167]

It is of interest that the continued intramuscular administration of long acting pitressin in oil to patients with congestive heart failure produces a clinical picture resembling refractory heart failure until the hormone is discontinued[15] And in patients with low sodium concentration in the plasma and a clinical picture of intractable heart failure, abnormal retention of water occurs even when there is no positive sodium balance Since other factors besides dehydration and increased osmotic pressure evoke the secretion of ADH[III] the abnormal retention of water in heart failure or certain stages of heart failure may be initiated through other mechanisms besides sodium retention[III] This is strikingly indicated by retention of water instead of its diuresis in certain patients with heart failure despite a low sodium concentration and consequent reduced osmolarity of the extracellular fluid Antidiuresis may thus be stimulated by other factors besides extracellular hypertonicity, perhaps an inadequate effective blood volume[87] or cardiac output

Other hormones and humoral agents have been implicated as possible factors in the diminished renal excretion of sodium and water Vasoexcitor material (VEM)[87] and renin[10] have been found in the renal venous blood and vasodepressor material (VDM) in the hepatic venous blood of patients with congestive heart failure[87] However there is no evidence that these substances are concerned with the formation of edema in heart failure

Cellular Changes in Renal Tubules The renal tubule cells perform work in the reabsorption of sodium from the tubule lumina Cellular metabolic processes and enzymes such as carbonic anhydrase and succinic dehydrogenase are concerned with the production of energy and its utilization in the performance of sodium reabsorption Our knowledge of these processes is still too primitive to permit an answer as to the possible action of heart failure on the renal tubule cell, either by its effect on the renal blood flow or oxygen supply or by some other means

Exercise and Renal Excretion of Sodium

Exercise is the commonest stress in the normal individual Exercise produces a

prompt retention of sodium and water in the normal individual and unless the exercise is severe there is little or no change in renal hemodynamics[134] (But see also Freeman et al[43]) Sodium and water retention may be regarded as an adjustment to body stress such as that represented by exercise Sodium water retention occurs in patients with heart failure even when they are at rest but the retention is greatly magnified by exercise[16] [redacted] Because of the qualitative similarity of the sodium water retention with exercise and in heart failure a similar mechanism has been sought for both[116] However the mechanism by which exercise produces renal retention of sodium and water either in the normal person or in the patient with heart failure is still conjectural It is to be noted that sodium excretion diminishes with exercise although the cardiac output increases But the sodium retention may indicate that though the cardiac output is increased it is at least temporarily inadequate for the augmented needs of the exercising muscles

Possible Stimulus and Receptor Sites for Renal Retention of Sodium and Water

Not only [redacted] there uncertainty as to the particular *renal mechanism* responsible for abnormal retention of sodium and water but there is an equal lack of understanding as to the stimulus which induces such retention Among the *possible* stimuli initiating such retention the following have been considered (1) inadequate cardiac output (2) diminution in effective circulating blood volume (3) diminution in cerebral blood flow (4) increased volume and pressure in various possible receptor areas of the venous system (5) redistribution of blood from the arterial to the venous side (6) diminished mixed venous oxygen concentration (7) anoxia of various body cells or of renal tubule cells

Renal retention of sodium is induced in a variety of physiologic conditions and abnormal states other than congestive heart failure[29] In normal persons the erect posture[41] sitting[149] or tilting the body toward a head up position[11] and exercise[135] result in a diminution in sodium and water excretion Sodium retention has also been observed following the application of tourniquets to the four extremities or to the thighs alone[158, 169, 73, 46] and following obstruction and venous congestion at various sites of the inferior and the superior vena cava, previously discussed[16, 75, 5] [redacted] (p 171) These varied observations have been interpreted by different observers to indicate that retention of sodium and water is stimulated either (1) by a reduction in effective blood volume due to pooling of blood in the lower extremities or other body areas with consequent transudation of plasma water out of the capillaries (2) by a reduction in cardiac output since reduction in effective blood volume is translated into reduced venous return and cardiac output or (3) by diminished cerebral blood flow due to diminished cardiac output or cerebral vasoconstriction such as occurs when an individual is in the upright position[116] Bleeding of normal dogs[81] or the occurrence of hemorrhage in pathologic states[19] is associated with a decline in sodium excretion which could be attributed to diminished effective blood volume or cardiac output

The above mentioned changes in excretion of sodium and water with postural changes the application of venous tourniquets and obstruction of various sites of the caval systems have suggested that changes in volume and pressure in some local area of the venous circulation might serve as the stimulus to renal retention of sodium and water Such a site might represent a volume regulator i e [redacted] regulator of the circulating blood volume besides that of the hypothalamic pituitary axis Lewis and associates[80] observed that in normal subjects in the sitting position compression of the neck by a blood pressure cuff inflated to 20 mm Hg or more induced a marked increase in sodium excretion but this did not occur in patients with heart failure[8] These findings suggested that the brain contained the receptor site for the regulation of volume by modifying the renal excretion of sodium and water and that this regulator was defective in a patient with heart failure because of a more powerful mechanism favoring sodium retention Compression of the legs by elastic bandages resulted in increased sodium excretion which was attributed to a redistribution of blood or extracellular fluid resulting in stimulation of a volume-regulating receptor area in the cranial cavity[117] On the other hand no further increase in sodium excretion occurred when the head was tilted after neck compression in subjects who were sitting and no increase in sodium excretion occurred when the neck was compressed in recumbent subjects Netravisesh[103] was unable to confirm

the reported findings of increased sodium excretion following compression of the neck

Observations in cases of high-output failure and notably in arteriovenous fistula, suggested that sodium retention may be stimulated by a redistribution of blood from the arterial to the venous side When an arteriovenous fistula is closed the high cardiac output is diminished but the excretion of sodium is increased This appears to contradict the theory that a fall in cardiac output diminishes sodium excretion But one may maintain that the high output in arteriovenous fistula is inadequate for tissue needs, whereas the lower cardiac output which occurs when the fistula is closed provides a more adequate supply of blood for the tissues How the kidneys sense that the higher output is inadequate and therefore retain sodium and water is unknown It seems that the initial stimulus must arise in the area of the body distal to the fistula which at first fails to obtain its needed blood flow because of the shunting of blood or because of venous congestion of that area It has also been suggested that the lowered peripheral resistance in arteriovenous fistula permits easier egress from the arterial to the venous system with a redistribution of the circulating blood volume in favor of the venous side This redistribution of blood to the venous side has been postulated to be the stimulus for retention of sodium and water in arteriovenous fistula as well as after postural change to the upright position, after the application of tourniquets and presumably in congestive heart failure[4]

In patients with low cardiac output the arterial oxygen concentration is usually normal but the oxygen concentration of mixed venous blood is diminished Renal retention of sodium and water has been related to the latter presumably because a diminished oxygen content of venous blood denotes a deficiency in oxygen supply or oxygen tension in the tissues However in high-output heart failure sodium retention occurs even though the oxygen content of mixed venous blood is higher than normal Thus sodium retention cannot be related to the *absolute* value of the mixed venous oxygen On the other hand the mixed venous oxygen is lower after heart failure in conditions of high cardiac output than it is before failure occurs

Hypoxia of various body cells would appear to be a plausible stimulus for sodium retention since hypoxia seems to be a consequence of the inadequate cardiac output which characterizes congestive heart failure However acute experimental hypoxia does not reduce the glomerular filtration rate in normal subjects nor does it further diminish the low filtration rate in patients with congestive heart failure[11] In fact breathing a low oxygen mixture caused an *increase* in sodium excretion[11] However, it is questionable whether the degree and brief duration of the experimental hypoxia duplicate the conditions of possible mild chronic cellular hypoxia in heart failure Furthermore the increased excretion of sodium may be due to hyperventilation induced by breathing air with low oxygen concentration

Hypoxia of the liver in heart failure has been invoked as a possible mechanism to account for water retention Vasodepressor material (VDM) is formed by the liver as a result of hypoxia in the experimental animal and produces antidiuresis by stimulating the posterior pituitary to secrete antidiuretic hormone Hypophysectomy abolishes the antidiuretic effect of VDM

Hypoxia or other disturbances associated with heart failure may alter cellular metabolism or cellular osmolarity There is evidence that alterations in cellular osmolarity may initiate renal mechanisms responsible for electrolyte and water retention[13, 154, 93]

The various observations mentioned above do not permit a definite choice of stimulus or mechanism responsible for the retention of sodium and water in heart failure Many of the experimental observations on sodium water retention have dubious applicability to the problem in congestive heart failure Differences in acute versus more prolonged experiments suggest caution in utilizing the experimental findings to interpret mechanisms in a chronic state such as congestive heart failure There is some doubt whether the stimulus to sodium water retention in patients with heart failure is the same as that in normal individuals That certain changes in sodium and water excretion occurring with change in posture and with compression of the neck are not observed in patients with heart failure[30, 37] has already been mentioned Another difference concerns the diurnal variation in sodium water excretion In normal persons maximum excretion of sodium and water occurs during the day in patients with heart failure during the night[37] Whereas

venous congestion of the legs or a phlebotomy of 450 to 700 cc of blood decreased sodium excretion in normal individuals they had variable effects on sodium excretion in patients with congestive heart failure[79] There was some evidence that the diminished unchanged or increased sodium excretion in these experiments was related to corresponding changes in cardiac output[80]

For the present this writer favors the theory that in heart failure the abnormal renal retention of sodium and water is the consequence of an inadequate cardiac output[11, 43, 44] This may act by causing anoxia of the liver of the pituitary and adrenal cortex of the renal tubule cells or of other organs or by disturbing volume and pressure relations in various segments of the venous system A reduction in effective blood volume is significant only insofar as it impairs the adequacy of the cardiac output Maintenance of a normal cardiac output is apparently carefully guarded by bodily homeostatic mechanisms[43] In heart failure the retention of sodium and water by the kidneys may represent a compensatory mechanism for restoring the cardiac output by increasing the circulating blood volume and venous return This hypothetical statement is not invalidated by the fact that the compensatory mechanism may itself be responsible for clinical symptoms for example many of the clinical features of shock are due to compensatory vasoconstriction secondary to diminished cardiac output More definite understanding of the mechanism responsible for sodium water retention in heart failure must probably await better knowledge of intracellular metabolism and especially of intrinsic mechanisms whereby tubule cells regulate the excretion of water and electrolytes

THEORIES OF MECHANISM OF HEART FAILURE

THE BACKWARD FAILURE THEORY

The backward failure theory maintains that the clinical manifestations of congestive heart failure are due to passive engorgement of the venous tributaries caused by a backward rise in pressure upstream from (i e proximal to) the failing cardiac chambers[81]

The backward failure theory was based on (1) experimental studies of the circulation (2) pathologic observations and (3) clinical observations

Correlation of Experimental Circulatory Studies with Backward Failure Theory

The studies of Starling[135] Straub[143] and others on the heart lung preparation and with similar experimental circulatory set-ups showed that the important cardiac and circulatory disturbances occurred *behind* the experimental obstruction or lesion while the abnormalities in front of or downstream from the lesion were only temporary and rapidly compensated (Chapter 4) Thus when the outflow from a cardiac chamber is obstructed or when the heart begins to fail the cardiac output is only slightly and temporarily diminished The affected chamber dilates contracts more forcefully because of the consequent lengthening of the cardiac fibers and thereby restores the normal output The venous pressure remains normal This corresponds to the clinical state of compensated heart disease

With increasing fatigue of the heart the pressure within the cardiac chambers becomes so elevated that the venous return to the heart is embarrassed Now the venous pressure rises i e backward from the heart This corresponds to the clinical stage of congestive heart failure With fatigue of the chambers on the left side of the heart as with experimental aortic and mitral valvular lesions there is an increased resistance to inflow into the left atrium The venous pressure rises in the pulmonary veins and their tributaries in the lungs This corresponds to left sided heart failure With severe experimental mitral stenosis there is a rise of pressure in the pulmonary artery This places a strain on the right ventricle Its intraventricular pressure rises to overcome pulmonary arterial resistance Eventually this rising pressure is transmitted backward until the venous pressure in the venae cavae and their tributaries is elevated This corresponds to right sided heart failure

The increased venous pressure according to Starling[135] promotes cardiac filling by maintaining a pressure difference between the great veins and the atria This rise in venous pressure serves as a compensatory mechanism by which the cardiac output is maintained at relatively normal or slightly diminished levels These and similar observations with

individual experimental valvular lesions were interpreted to indicate that the sequence from earliest cardiac fatigue to frank heart failure is characterized by a rising pressure in the cardiac chambers retrograde from the site of disturbance into the venous system Recent determinations, by intracardiac catheterization, of the venous pressure and of the pressures within the cardiac chambers of patients with heart failure have confirmed these pressure changes as postulated by the backward failure theory For in left sided heart failure there is a pronounced elevation in left atrial pulmonary venous capillary and arterial pressure and in right ventricular systolic and pulse pressure, in right sided heart failure there is an elevation of the right ventricular diastolic pressure the right atrial and the peripheral venous pressure[9] (p 165)

Pathologic Support for Backward Failure Theory

Pathologic observations indicate that heart failure is characterized by venous congestion involving the organs proximal or behind the failing chamber and not by ischemia in front of or distal to that chamber In cases of left ventricular heart failure only or predominantly the lungs show evidence of capillary and venous congestion as if there were "back pressure" from the failing left chambers In cases in which the right ventricle fails, the capillary and venous congestion is located in organs which would experience a rise in venous pressure "backward" from the right side of the heart viz the liver spleen intestines kidneys skin and so on Furthermore, the symptoms and signs of congestive heart failure appear to arise in these sites of venous congestion

Clinical Observations Supporting Backward Failure Theory

The backward failure theory appears to conform with the observation of isolated left and isolated right ventricular failure and with the usual sequence of development of the individual symptoms of left- and right sided failure Thus if the left ventricle fails and the right is competent the venous congestion is localized in back of the left chambers, i e in the lungs the elevated venocapillary pressure is localized to the lungs and the only symptoms are those referable to pulmonary congestion namely dyspnea orthopnea cardiac asthma, pulmonary edema and cough The systemic venous pressure is not elevated and there are no symptoms referable to systemic venous congestion Similarly, there may be isolated right ventricular failure with venous congestion, elevated venous pressure and corresponding clinical features confined to organs drained by systemic veins

If the clinical features of heart failure were due exclusively directly or indirectly, to forward failure i e to an inadequate cardiac output, failure of the left ventricle should lead either to symptoms referable to organs supplied by the left ventricle (e g , brain extremities abdominal viscera, but not the lung) or to symptoms referable to both the systemic and pulmonary circulation

Finally in the common forms of heart failure due to coronary artery disease, hypertension or aortic and mitral valvular disease the sequence of development of symptoms appears to support the backward failure theory The first symptom is breathlessness which may be related to congestion of the lungs Later as pressure rises not only in the pulmonary vessels but in the right ventricle, the latter fails the right ventricular diastolic the right atrial and the systemic venous pressures rise (in a backward sequence from the failing chambers) and the symptoms of right ventricular failure appear

THE FORWARD FAILURE THEORY

The fundamental basis for the forward failure theory is the presence in heart failure of an inadequate cardiac output Formerly this theory explained symptoms and signs in each individual organ as the direct consequence of insufficient blood to that organ In its more recent form, symptoms of congestive heart failure are attributed only in part to inadequate blood flow to individual organs but *chiefly to a renal retention of sodium and water* because of inadequate blood flow to the kidneys Emphasis is placed on a prolonged deficiency of cardiac output relative to the requirements of the tissues rather than on an absolute diminution in cardiac output[141] The cardiac output may be adequate when the patient is at rest and he is asymptomatic, yet during activity the output may even increase but is inadequate for the increased bodily demands and symptoms of heart failure appear In the presence of advanced heart failure symptoms such as weakness and fatigability, believed to result directly from inadequate blood flow (to the muscles) are masked by

dyspnea, orthopnea and edema believed to result indirectly from impaired renal excretion of sodium and water. When the latter symptoms are alleviated by the restriction of sodium and by the administration of mercurial diuretics, weakness and fatigability may become more apparent.

The forward failure theory is supported by the usual finding of a diminished cardiac output, by the finding of a diminished renal blood flow, by the impairment of renal excretion of sodium and water and by the fact that the clinical phenomena of congestive heart failure are dependent on an abnormal retention of sodium and water. According to the forward failure theory, the impaired renal excretion is related to the diminished cardiac output and consequent reduction in renal blood flow. Merrill[100] found that the renal blood flow in patients with heart failure was reduced to one third to one fifth of normal. Since the reduction in renal blood flow was greater than the reduction of cardiac output, there appeared to be a specific diversion of blood away from the kidney. Other studies confirmed these findings and disclosed that the glomerular filtration rate was also reduced but not as much as the renal blood flow. Diminution of renal blood flow and glomerular filtration was related to the degree of reduction in cardiac output but bore no relation to the venous pressure; these findings were interpreted to support the forward failure and not the backward failure theory.

Elevated Venous Pressure Versus Renal Retention of Sodium and Water

A large measure of the disagreement between the proponents of the backward failure and of the forward failure theories concerns sequence of development and the relative importance of renal retention of sodium and water as compared with the elevation of venous and capillary pressure in the production of edema and other cardinal symptoms of heart failure. The occurrence and severity of edema cannot always be correlated with the presence or degree of elevation of venous pressure. On the other hand, an elevated venous pressure at rest or with mild exercise is the rule in heart failure associated with edema.

Observations by Warren and Stead[15] on the appearance of heart failure were interpreted to indicate that salt and water retention in the body tissues precedes the development of an elevated venous pressure. They administered 9 to 12 gm of sodium chloride by mouth to patients recently recovered from heart failure and made daily observations of weight and frequent observations of the venous pressure. A significant weight gain, presumably due to salt-water retention, occurred when the venous pressure was still normal; elevation of venous pressure occurred a few days later. Similar observations were reported by Goldman and Bassett.[illegible] However, the findings could also be interpreted to support the backward failure theory, for the water retention causing weight gain could have first been limited to the left heart chambers and pulmonary circulation, and there may have been a rise in pulmonary venous pressure before a rise in systemic venous pressure was apparent. Furthermore, it is often difficult to distinguish a time difference in the development of elevated venous pressure and gain in weight due to sodium water retention, both apparently occurring virtually simultaneously.[240, 111]

When digitalis is withdrawn from a patient with heart failure on a low sodium intake, the venous pressure rises without an accompanying gain in weight.[111, 121] These observations likewise cannot be interpreted to support the primary importance of either elevated venous pressure or sodium water retention in heart failure. The use or discontinuation of a therapeutic agent can modify one or the other of these factors. When digitalis is withdrawn from a patient whose symptoms of heart failure are under control and who is receiving a minimal quantity of sodium, there is a further deterioration of cardiac function resulting in a further reduction of the cardiac output. This may lead to an elevation of venous pressure because the undigitalized deficient heart can no longer accept and eject the venous return. On the other hand, weight gain and edema may not occur because the sodium water retention necessary to its formation is artificially inhibited by the low sodium intake.

CRITICISMS OF BACKWARD FAILURE AND FORWARD FAILURE THEORIES

There can be no "backward failure" without "forward failure" in a continuous circulation. Hence the contrast of terms should be abandoned. The term "backward failure" is a confusing one in that it implies a *direction* of flow when actually it refers to a sequence of *locations* of venous congestion. Even if the

symptoms of heart failure appear to be due to venous congestion and rising pressure behind a failing chamber the backward failure theory omits a series of preceding or almost simultaneous events, including the renal retention of sodium and water, which occurs after the initiation of heart failure and without which such congestion could neither occur nor persist Heart failure could not produce a persistent rise in pressure behind the failing chamber unless simultaneously or very soon thereafter there occurred an increase in circulating blood volume Starr et al[140] observed only a slight increase in venous pressure following acute and chronic damage to the dog s right ventricle Starr[139] also noted that immediately after death the static blood pressure in the heart and vessels, i e in the absence of the heart beat was three times as high in subjects who had died of heart failure as in those without heart disease These observations were interpreted to indicate that the venous congestion and elevated venous pressure in heart failure were due not to stasis behind the weakened chamber but essentially to increased blood volume in the distensible veins and to venoconstriction

The forward failure theory does not satisfactorily account for inconsistencies between the cardiac output and the occurrence and severity *of symptoms of congestive heart* failure Sodium retention cannot always be correlated with reduction in cardiac output and with reduction in renal blood flow Sodium water retention per se does not account for the localized rise in venous pressure in the pulmonary circulation in left sided heart failure and in the systemic veins in right sided heart failure Warren and associates[151] noted that shortly after the intravenous injection in dogs of normal saline in an amount equal to body weight, over a period of six to eight hours the extracellular fluid volume was more than doubled but the blood volume and venous pressure were virtually unchanged This suggests that a persistent increase in blood volume and in venous pressure does not follow increased sodium and water intake unless heart failure is present The forward *failure theory does not clearly* account for the occurrence of isolated left-sided heart failure or for the sequence of development of symptoms in progressive left sided and subsequent right-sided heart failure Finally, the clinical picture which characterizes a definite fall in cardiac output is that of shock, not that seen in congestive heart failure

THE MECHANISM OF CONGESTIVE HEART FAILURE

On the basis of the observations of changes in hemodynamics and in electrolytes and fluid in congestive heart failure described in the preceding portion of this chapter the following mechanism of heart failure appears most probable But it must be stressed at the outset that there are still many important gaps in our knowledge and that any theory of heart failure at the present time suffers from considerable speculation

Initial Disturbances in Heart Failure

When a chamber fails it no longer ejects as much blood as it normally does with a given inflow Consequently, the output is diminished and the blood residual in the chamber is increased The end diastolic pressure rises Elevated ventricular diastolic pressure is associated with corresponding elevation of atrial and venous pressure While deficient emptying of the failing chamber may be followed by temporary increase in these pressures the maintenance of these increases depends on mechanisms which are uncertain at *the present time Otherwise, the falling output* would result in a lower arterial pressure diminished venous return and eventual reduction of the venous atrial and ventricular diastolic pressures The diminished cardiac output, the elevated pressure in the failing chamber or the elevated venous pressure may initiate mechanisms which maintain the elevated pressures and the disturbances in blood flow and distribution of water and electrolytes which characterize heart failure

These mechanisms may be regarded as homeostatic mechanisms which restore the cardiac output when this tends to become inadequate because of physiologic or pathologic disturbances In congestive heart failure an augmented circulating blood volume serves to restore the cardiac output when the fall in output is moderate and sufficient time elapses to *permit the development of this compensatory* mechanism *The symptoms of congestive heart failure are due in large measure to difficulties imposed by the compensatory mechanisms and not directly to a deficient output* hence there is

no close correlation between the cardiac output and severity of symptoms except in advanced cases

Homeostatic Mechanisms Controlling the Cardiac Output

The fundamental function of the heart is to maintain an adequate output of blood for the tissues under all physiologic circumstances. When the heart fails a variety of compensations are evolved which tend to restore this vital function. Consequently the cardiac output is maintained long after serious circulatory threats and disturbances arise just as the pH of the blood remains constant despite disorders threatening its acid base balance and just as the blood urea remains normal even when there is moderately severe renal impairment

The following compensatory mechanisms may restore a deficient cardiac output or may otherwise serve to maintain an adequate blood supply to vital organs

1 *Tachycardia and Cardiac Enlargement* These accommodative mechanisms which increase the cardiac output have been previously discussed (Chapter 4) Like all compensations cardiac enlargement is valuable in that it preserves a vital function in this instance a normal cardiac output It is disadvantageous because it signifies the expenditure of a circulatory reserve and because it is associated with inefficiency in the need and utilization of oxygen

2 *Arteriolar Vasoconstriction* Arteriolar vasoconstriction occurs when there is a reduction in cardiac output Its compensatory effect is not to restore the cardiac output to normal but to redistribute the diminished output in such a manner as to maintain an adequate blood flow to vital areas Thus blood is diverted from the periphery and abdominal viscera to the brain and heart

Arteriolar vasoconstriction is an important compensatory mechanism in conditions which cause such a rapid and intense fall in cardiac output that actual restoration to normal is impossible The associated clinical picture is acute circulatory failure or shock (Chapter 12) But in chronic congestive failure in which the diminution in cardiac output is relatively moderate and occurs gradually arterial vasoconstriction and redistribution of blood are of minor importance for other mechanisms can be employed which are capable of restoring the cardiac output to adequate levels

Arteriolar vasoconstriction may serve not only to redistribute better the diminished cardiac output but also to initiate slower mechanisms which tend to restore an adequate output In particular the kidney undergoes arteriolar constriction whenever the cardiac output is diminished The resulting diminution in renal blood flow has been held responsible for the retention of sodium and water which helps to restore the cardiac output by increasing the blood volume and venous return In addition arteriolar vasoconstriction in various tissues results in a fall in capillary hydrostatic pressure which favors the absorption of interstitial fluid into the blood stream with a tendency to increase blood volume and cardiac output In cases of advanced heart failure in which the cardiac output falls significantly despite various compensatory mechanisms the blood pressure is usually maintained despite the fall in output This is possible only because of a compensatory increase in total peripheral resistance i e arteriolar constriction

The mechanism responsible for renal arteriolar constriction is uncertain It may be induced as part of a generalized splanchnic vasoconstriction which occurs when a diminished output inhibits the vasodepressor mechanism and the carotid sinus vagal arc Sympathetic stimulation has been regarded as excluded because the renal blood flow in congestive heart failure was not altered by a high spinal anesthesia[104] Humoral agents have also been invoked to account for renal arteriolar constriction in heart failure Renin has been demonstrated in the renal venous blood of patients with chronic congestive heart failure[10] Renal arteriolar constriction has also been attributed to the release of vasoexcitor material from the kidney due to renal hypoxia caused by an inadequate cardiac output[37]

3 *Increased Venous Return* The venous return over a period of time is equal to the cardiac output for the heart can only pump as much blood as it receives in a unit of time Factors increasing the venous return tend to increase the cardiac output The venous return may be augmented by (a) increasing the speed of the circulating blood or (b) increasing the circulating blood volume i e

the width of the stream returning at a given speed When the cardiac output falls or for some other reason is unequal to the demands of the tissues it may be made sufficient by compensatory mechanisms which increase the venous return either by accelerating the speed of the circulation or by augmenting the volume of the circulating blood

(a) *Increased Speed of Circulating Blood* During exercise or febrile states, the cardiac output is increased largely by acceleration of the speed of the circulation In certain pathologic states which render the ordinary output inadequate for body requirements, the abnormally high outputs required are attained largely by acceleration of circulating speed e g in cases of hyperthyroidism anemia, beriberi and arteriovenous fistula A diminution in peripheral resistance permits the more rapid circulation (p 186)

(b) *Increased Blood Volume* In most conditions leading to chronic congestive heart failure cardiac enlargement first develops and maintains an adequate output despite cardiovascular disturbances When this compensatory mechanism is no longer effective or when it is insufficient from the beginning restoration of cardiac output may follow an increase in the circulating blood volume In the heart lung preparation constriction of the aorta reduces the cardiac output but the output may be restored first by cardiac dilatation and when this is inadequate by an increase in the venous return to the heart In humans also an increase in blood volume by intravenous infusions augments the cardiac output

Similarly when the cardiac output falls because of failure of the heart, a progressive enhancement of the circulating blood volume tends to restore the cardiac output *Thus the blood volume may be represented as a fundamental homeostatic mechanism for maintaining an adequate cardiac output* The increased blood volume in congestive heart failure is due both to an increase in erythrocytes and to an enhanced plasma volume (p 220) The former may be the result of relatively inadequate blood flow to the bone marrow with an anoxic stimulus to erythrogenesis Increase in plasma volume is due essentially to abnormal renal retention of sodium and water

Eventually, these homeostatic compensatory mechanisms no longer maintain an adequate cardiac output This is due to the fact, noted by Starling[123] that there is a peak beyond which an increase in venous return does not further enhance the cardiac output (p 86) Progressive increase in the volume of circulating blood and of the venous return eventually overloads the failing heart Thereafter despite an augmented blood volume the cardiac output diminishes In part, at least failure of the increased venous return to be translated into greater cardiac filling and greater output is due to a pronounced rise in pressure within the cardiac chambers Although the venous pressure may be greatly elevated the venoatrial pressure difference which is the effective filling pressure, is diminished in this advanced stage of congestive heart failure[124]

In the late stages of congestive heart failure the cardiac output is low despite the body s efforts at compensation Arterial vasoconstriction and redistribution of the reduced output serve to maintain an adequate blood supply to vital organs Venous congestion and slowing of the blood stream are notable features The slowing permits a greater extraction of oxygen from each unit of blood (i e the arteriovenous oxygen difference is larger than normal) and this partly counterbalances the diminished blood flow Actual measurements with the aid of cardiovascular catheterization have shown an increased arteriovenous arterial oxygen not only in the general circulation but al o in the renal and hepatic circulations

The Relation of Increased Blood Volume to Venous Return and Venous Pressure

The retention of sodium and water over a period of time leads to an increase in the circulating plasma volume in patients with heart failure The greater blood volume is accommodated by an enlarged capacity of the venous system This augmentation of the blood volume denoting a wider stream of blood is translated into an increased venous return to the heart an effect similar to that of an intravenous infusion or transfusion

A clear distinction should be made between an increased venous return and an increased venous pressure The venous pressure is the resultant of two forces the venous return and the capacity of the receiving cardiac chamber to accept and eject that venous return A rise in venous pressure occurs when a cardiac chamber cannot handle its venous return

Rarely this occurs with a normal cardiac chamber if there is a sudden and enormous increase in the venous return; more commonly the venous pressure rises in the presence of a diseased or strained chamber with a venous return which is only moderately increased, e.g., by a rapid intravenous infusion.[2,107] Conversely, the reduction of an elevated venous pressure may occur either because the venous return is diminished (e.g., by phlebotomy, the application of tourniquets or by mercurial diuretics) or because the efficiency of the diseased heart is improved, e.g., by digitalis.

The cause of the elevated venous pressure in heart failure and its relation to the enlarged blood volume are disputed. According to the backward failure theory as delineated by Starling[138] the following sequence obtains:

Cardiac failure ⟶ elevated venous pressure and venous congestion ⟶ compensatory arteriolar constriction ⟶ anoxia of bone marrow ⟶ increased blood volume.

The hypervolemia, according to this concept, is secondary to the elevation in venous pressure. But it seems incredible that there can be more than a transient rise in venous pressure and venous congestion unless the blood volume is first increased. For as blood became impounded behind the failing chamber, the cardiac output and venous return would diminish and thus relieve the venous congestion and reduce the elevated venous pressure. Without sodium water retention by the kidney there is no increase in blood volume and without the latter there is no pulmonary or systemic venous congestion and no elevation in venous pressure. The elevated venous pressure cannot persist except by virtue of the augmentation of blood volume. This concept is supported by the experiments of Starr, Jeffers and Meade[140] who found no elevation of venous pressure following severe damage to the right ventricle, and by the observations of Starr[139] who found a persistent elevation of the venous pressure post mortem in patients who had died from congestive heart failure. The former experiments demonstrated that failure of a chamber per se may not cause an elevated venous pressure and the latter observations indicated that even when the factor of cardiac contraction is eliminated by death, the elevated venous pressure of chronic heart failure persists because of the augmented blood volume. Thus sodium water retention, increased blood volume and increased venous pressure are sequential integrated events in heart failure, not independent factors of varying importance. Furthermore, failure of the heart must mean an initial reduction in output as well as a damming of blood within and proximal to the failing chamber. Therefore anoxia of bone marrow or other tissues and organs could be as reasonably attributed to reduced cardiac output (forward failure) as to arteriolar constriction compensatory to elevated venous pressure (backward failure).

According to the forward failure theory the following sequence is postulated:

Cardiac failure ⟶ decreased renal blood flow ⟶ decreased renal excretion of sodium and water ⟶ increased extracellular fluid and increased blood volume.

Merrill[109] accepts this latter sequence of forward failure to account for the increased blood volume but invokes backward failure to account for elevated venous pressure behind the failing chamber. Warren and Stead[15] likewise accept the forward failure sequence leading to hypervolemia but attribute the elevated venous pressure first to venous vasoconstriction and second to increased blood volume. Clinical observations of engorged veins belie the existence of venoconstriction in congestive heart failure. This discrepancy has been explained by assuming increased venous tone in the deeper veins with consequent expulsion of blood into the more distensible superficial veins which appear engorged.[3] However, this concept in itself fails to explain why, if venoconstriction and hypervolemia are the causes of increased venous pressure, the venous pressure can be normal in the systemic circulation and elevated in the pulmonary system when the left side of the heart fails.

According to the mechanisms which I have outlined above, the sodium and water retention by way of the kidney occurs as a direct consequence of the initial reduction in cardiac output but not necessarily as a direct consequence of diminished blood flow to the kidney. Hypervolemia results from sodium water retention and maintains an elevation of venous pressure. Hypervolemia increases the venous return. *The venous pressure rises at the entrance to those chambers which are incompetent to receive and expel this augmented return.* Arteriolar vasoconstriction tends to develop

but it has no significant effect on the venous pressure in chronic heart failure Its chief purpose is to redistribute a diminished cardiac output in favor of the more vital organs, and perhaps to promote changes in renal function which result in increased blood volume (See also p 185 for effects of exercise)

Relation of Venous Return and Venous Pressure to Cardiac Output

There is no invariable relationship between *venous return and cardiac output* although as a rule an increase in the former enhances the latter But when a diseased chamber becomes overloaded a temporary further increase in the venous return may be followed by no increase or a reduction in the cardiac output *The relationship of venous pressure to cardiac output* is much more indirect If no other factors were operative an increased venous pressure would tend to elevate the cardiac output But changes in venous pressure are the result of other factors and these latter not the venous pressure control the output Thus in an overloaded failing heart reduction in the *venous return by phlebotomy may diminish* the venous pressure and increase the cardiac output by permitting the heart to function more efficiently But in the presence of a normal heart reduction of the venous return by hemorrhage is associated with an unchanged or diminished venous pressure and a reduction in cardiac output [8, 20] Similarly the venous pressure may not change during temporary closure and reopening of an arteriovenous fistula although the cardiac output is quite different in the two states because the healthy heart can handle the smaller or the larger venous return equally well

In summary the cardiac output increases as the venous return increases provided that the competence of the heart is normal or only moderately impaired With advanced myocardial incompetence, increased venous return may be followed by a reduction in cardiac output On the other hand the venous pressure may diminish, remain constant or increase as the cardiac output increases depending on the ratio of the venous return to the competence of the heart in handling the venous return

PATHOGENESIS OF LEFT SIDED AND RIGHT SIDED HEART FAILURE

In certain stages of coronary heart disease hypertension and rheumatic aortic and mitral valvular disease, the left chambers of the *heart fail while the right chambers are still* unimpaired The early reduction in left sided cardiac output or the initial elevation in pressure in the failing chambers and the pulmonary veins leads to a retention of sodium and water with its tendency to increase the circulating blood volume and restore the diminished cardiac output The normal right *chambers are competent to receive and eject* the venous inflow Right ventricular output now returns to the left chambers of the heart but the failing left chambers cannot competently accept and eject this venous return The disparity between inflow and capacity to put out blood leads to an increase in pulmonary venous pressure due to the increased *resistance of blood dammed up proximal to the* diseased chamber *The pulmonary venous pressure rises, not because of a 'backward pressure but because the increased venous return, moving in a forward direction, cannot be passed along with normal speed by the failing chamber* The augmented blood volume concentrated in the pulmonary vascular bed leads to the symptoms of left sided heart failure

In the earliest stages of isolated left-sided heart failure the increased blood volume tends to increase the pulmonary venous return to restore a normal left atrial and left ventricular output A normal right ventricular output is added to the residual in the pulmonary vascular bed and left cardiac chambers which was not ejected by the incompetent left chambers There is thus a constant engorgement of the pulmonary vascular bed which tends to stimulate the failing left heart to normal output But when these chambers become overloaded, the output may fall despite pronounced pulmonary congestion and increased pulmonary venous pressure Under such circumstances the blood flow is reduced because the rise in venous pressure does not keep pace with the increased resistance to blood flow at the site of the failing chamber

Right-sided heart failure may appear as an isolated syndrome due to pulmonary or pulmonary vascular disease or as a result of congenital cardiac disease or constrictive pericarditis More commonly right sided heart failure results from and is associated with left-sided heart failure In cases of intrinsic pulmonary or pulmonary vascular disease there is an increased resistance to blood flow in the pulmonary circulation, but compensa

tory dilatation and hypertrophy of the right ventricle maintain a normal cardiac output and consequently an elevated pulmonary arterial pressure. In left sided heart failure the increased resistance to right ventricular outflow is in the pulmonary veins and capillaries. Eventually the right ventricle fails and its residual volume and diastolic pressure increase. Right atrial and central venous pressure rise. Renal retention of sodium and water increases the blood volume and tends to increase the venous return and cardiac output. Now the failing right cardiac chambers are unable to accept and discharge the venous return and the systemic venous pressure rises. In constrictive pericarditis the venous pressure rises because the constricted ventricle cannot relax in diastole and accept the venous return normally. The engorgement of the systemic veins and their elevated venous pressure result in the clinical features of right sided heart failure.

Relation of Exercise to Pathogenesis of Symptoms of Heart Failure

The commonest first symptom of congestive heart failure is breathlessness on exertion. In the earliest stages there may be no symptoms at all unless the patient is engaging in exercise. This fact has been used to account for some of the apparently paradoxical findings in heart failure.

Thus the observation of normal cardiac outputs in some patients with heart failure is attributed by forward failure advocates to the fact that the determinations are made with the patient at rest when his cardiac output may in fact be normal. The presumption is that the output becomes inadequate during exercise at which time symptoms appear.[80] But since dyspnea occurs promptly it is necessary to explain how the inadequacy of output is so rapidly translated into symptoms. According to the forward failure theory this deficient output during exercise leads to a diminished renal plasma flow,[101] an increased tubular reabsorption of sodium[125] and a consequent salt water retention by the kidney. But it is implausible that this mechanism would produce an immediate augmentation of pulmonary congestion sufficient to induce clinical symptoms.

The adherents of backward failure explain the occurrence of dyspnea on exertion by the effects of exercise on the venous pressure.[66] The venous pressure is normal when the cardiac patient is at rest but increases as a result of back pressure during exercise. Such repeated transitory elevations of venous pressure are viewed as reducing the effective blood volume causing compensatory arteriolar constriction and in some way stimulating an eventual increase in blood volume. Or else the elevations of venous pressure increase renal venous pressure and cause renal retention of sodium and water. But this explanation likewise fails to explain the prompt development of dyspnea during exercise. Even though there may be an elevated systemic venous pressure during exercise[3] it does not explain how this could immediately increase the pulmonary congestion which is the basis of dyspnea (p 190)

The dyspnea which occurs promptly on exertion in patients with early left-sided heart failure can be explained according to the modified theory I have outlined. The left side of the heart has a limited reserve and a limited ability to handle an increased venous return. In early left sided heart failure a moderate pulmonary congestion exists even when the patient is at rest but the degree of congestion is below the threshold of causing clinical symptoms.

During exercise there is a prompt increase in the venous return. This increase is mediated entirely or almost entirely by an increased speed of circulation and not by any significant augmentation of circulating blood volume. The opening of vascular channels in the exercising muscle produces the equivalent of arteriovenous shunts which permit a speedier venous return to the heart. This mechanism of increasing the venous return unlike that of augmenting the blood volume is immediately significant.

According to principles already mentioned this increased venous return during exercise need have no effect on the systemic venous pressure if the right side of the heart is competent. But in reaching the low reserve left side of the heart it meets obstruction because of the inability of the incompetent left heart to receive and expel the enlarged return of blood. Pulmonary congestion occurs or if already present is increased and accounts for the prompt dyspnea. Because of the incompetence of the left side of the heart the initial increase in venous return under the stimulus of exercise may not be translated into an increased cardiac output. Hickam and Car

gill[69] found that in persons with left ventricular failure there is an elevated pulmonary arterial pressure which is further elevated during exercise but *there is little or no increase* in cardiac output

THE PATHOGENESIS OF HIGH OUTPUT HEART FAILURE

The pathogenesis of heart failure discussed above, refers to cases of primary heart disease in which heart failure is usually associated with some reduction in cardiac output Special features distinguish the development of heart failure in such conditions as hyperthyroidism anemia, beriberi, arteriovenous fistula osteitis deformans and severe pulmonary emphysema in which the cardiac output is elevated (See also discussion under individual diseases)

These conditions are all characterized by an increased tissue need for blood which can be compensated by an augmented cardiac output In patients with anemia and severe emphysema the increased need is due to the deficient oxygen content of the blood in those with hyperthyroidism it is due to increased metabolic requirements in those with arteriovenous fistula the need arises because short circuiting of blood deprives a large area of an adequate blood supply in those with beriberi a deficient content of thiamine is the apparent cause In cases of osteitis deformans the mechanism is that of arteriovenous fistula[35] The required compensatory increase in cardiac output is effected by an increased venous return The latter occurs only in part through an increased blood plasma volume and chiefly through an increased speed of the circulation The latter is made possible by a decrease in the peripheral resistance

In cases of heart failure due to cardiac or valvular disease the initial fall in cardiac output leads to peripheral vasoconstriction and increased peripheral resistance which inhibit speeding of the circulation Restoration of an adequate cardiac output can only be accomplished by augmentation of the blood volume In the high-output groups of cases the initiating disturbance begins in the periphery, not the heart and results in a diminished peripheral resistance which favors speeding of the circulation The diminished peripheral resistance may be due to the presence of a shunt (arteriovenous fistula) or to vasodilatation caused by hypermetabolism anemia and the like The quickened speed of circulation increases the venous return and *the cardiac output to the required level* In most of these conditions there is also some utilization of the compensatory effect of an increased plasma volume depending on the extent to which speed alone can satisfy the excessive demand for blood Thus an increased plasma volume appears to be stimulated when the compensatory increase in speed does not adequately elevate the cardiac output The need for this additional compensation may arise because the acceleration of the circulation diminishes the oxygen utilization per unit of blood flow

Heart failure occurs when the heart despite its enlarged output is no longer satisfying the exorbitant demands of the *tissues for blood When this happens* the same mechanisms described in the low output cases lead to sodium and water retention hypervolemia and increased venous return in an effort to attain the necessary output Increased splanchnic arteriolar constriction occurs but is usually insufficient to neutralize the diminished total peripheral resistance Eventually as above, the failing heart is unable to handle the increased venous return or to respond with an increased cardiac output At this point the cardiac output falls from its peak, but despite heart failure the output is still considerably in excess of the usual normal Plasma hypervolemia becomes associated with the increased speed of circulation In the low output cases hypervolemia is associated with retarded circulatory speed

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Chapter 9

THE PATHOGENESIS OF INDIVIDUAL MANIFESTATIONS OF CONGESTIVE HEART FAILURE

PATHOGENESIS OF CARDIAC DYSPNEA

Dyspnea has been defined as subjective distress associated with difficulty in breathing (p 142) The following discussion concerns not only the mechanisms responsible for the objective abnormalities in pulmonary respiration but also the cause of the accompanying subjective discomfort

The occurrence of dyspnea in heart failure has been related to three possible mechanisms

(1) *An inadequate cardiac output and blood flow to the respiratory center stimulates increased respiratory effort*

(2) *An accumulation of carbon dioxide, a reduction in oxygen or a diminution in the pH of the blood* produces dyspnea by stimulating the respiratory center and/or carotid sinus,

(3) *Pulmonary congestion causes rigidity of the lung* and impairs normal reflex breathing because of mechanical interference with pulmonary expansion and retraction

CEREBRAL BLOOD FLOW AND DYSPNEA

Dyspnea has been attributed to an inadequate cardiac output and consequent ischemia of the respiratory center [40] But dyspnea is an *early* symptom of left heart failure and in early heart failure the cardiac output is usually normal The cardiac output falls as heart failure advances Yet dyspnea may be alleviated when progressive heart failure affects the right as well as the left cardiac chambers In cases of acute circulatory failure (shock) there is a pronounced diminution in cardiac output with minimal or no dyspnea Comparative studies of the oxygen content of arterial and internal jugular blood in patients with cardiac dyspnea showed no increase in arteriovenous oxygen difference, as would be anticipated if there were slowing or insufficiency of the cerebral blood flow [3] Other observers have found the cerebral arteriovenous oxygen difference to be increased in most cases of heart failure Determinations of the cerebral blood flow by the nitrous oxide method indicated a reduction proportional to the diminution in cardiac output according to Scheinberg[105] and Moyer et al,[84] but cerebral oxygen consumption was virtually normal On the other hand, Novack et al [89] found the cerebral blood flow to be normal in congestive heart failure, as did Moyer et al [87] and demonstrated that the reductions previously reported were probably due to associated cerebral atherosclerosis Thus the occurrence of dyspnea in heart failure cannot be correlated with a reduction either in cardiac output or in the blood flow to the respiratory center

BLOOD CHEMICAL CHANGES AND DYSPNEA

Numerous observations indicate that chemical changes in the blood which might result from heart failure are not primarily responsible for cardiac dyspnea although they may contribute to its occurrence or increase its severity in advanced stages of heart failure The oxygen and carbon dioxide content and the pH of the blood are the pertinent factors Only the composition of *arterial* blood, which supplies the respiratory center and carotid body is significant But changes in venous blood could conceivably influence peripheral respiratory chemoreceptors reported to be present in the pulmonary arteries[109] or lungs [■] reports not, however supported by the more recent studies of Aviado et al [5]

Arterial Oxygen

Normally the arterial oxygen saturation is 95 to 99 per cent. Meakins and his co-workers[84] and Frazer and co-workers[41] observed *normal oxygen saturations in almost* all cases of cardiac dyspnea unless the heart failure was very severe or there were pulmonary complications. Cullen and co-workers[2] discovered no arterial anoxemia even after exercise in patients with slight or moderate heart failure associated with dyspnea. Although the arterial oxygen saturation is usually normal, it is slightly reduced to concentrations of 90 to 95 per cent in many cases.[85] *Because of the character of the* oxyhemoglobin dissociation curve in this concentration range, the arterial oxygen tension is significantly diminished even with slight reductions in oxygen saturation.[17] Nevertheless it is more relevant that in the majority of cases of heart failure dyspnea occurs when the arterial oxygen saturation and oxygen tension are normal.

These observations reveal that the common *form of cardiac dyspnea, which appears early* in the course of left-sided heart failure, is not due to a reduction in the arterial oxygen saturation or content. Furthermore low arterial oxygen contents in certain cases of congenital heart disease with cyanosis are frequently unaccompanied by dyspnea. Of course there are instances of heart failure with pulmonary complications or of congenital heart disease with cyanosis in which a very low arterial oxygen content is a contributing or major factor in dyspnea. But this is the exceptional, not the usual, pathogenesis of cardiac dyspnea.

Tissue anoxia may be present in heart failure, especially after exercise, even when arterial oxygen is normal. The presence of tissue anoxia is supported by the finding of a low venous blood oxygen tension. It would appear that this could contribute to dyspnea only if it affected pulmonary arterial or other unproven venous respiratory chemoreceptors. But venous hypoxemia denotes also tissue anoxia of the respiratory centers and this might increase the respiratory stimulus.

Arterial Carbon Dioxide

Similarly cardiac dyspnea cannot be attributed to an increase in arterial carbon dioxide. The concentration and tension of carbon dioxide in the arterial blood is actually reduced and not elevated.[40] The reduction is a secondary effect of the hyperventilation associated with dyspnea. Only occasionally, with extreme pulmonary congestion and edema or with severe pulmonary emphysema or other *extensive pulmonary complications, is there* an interference with carbon dioxide elimination and a consequent elevation of its concentration in the blood. In such instances it may contribute to hyperventilation and associated dyspnea. A reduction in arterial carbon dioxide tends to increase cerebral vascular resistance, but no significant reduction in cerebral blood flow has been found to result from altered arterial carbon dioxide in heart failure.[39]

Hydrogen Ion Concentration

The hydrogen ion concentration of the blood is either normal or slightly diminished (gaseous alkalosis) in cases of cardiac dyspnea due to pure left-sided failure.[4] Therefore arterial acidemia cannot be held accountable for this type of dyspnea. On the other hand when heart failure is associated with carbon dioxide retention due to extensive pulmonary disease, the hydrogen ion concentration in arterial blood increases (gaseous acidosis). A reduction in the pH of the blood may also result from the accumulation of fixed acids such as lactic and pyruvic acid in very advanced or terminal cases of heart failure with pronounced peripheral stasis or in cases of heart failure with renal insufficiency.[40] During exercise also patients in heart failure accumulate fixed acids more readily than normally.[, 85] I have seen a marked reduction in hydrogen ion concentration with clinical acidosis in patients in heart failure treated continuously with ammonium chloride. Under these special circumstances arterial acidemia may produce dyspnea by excessive stimulation of the carotid body and respiratory center. However, the dyspnea of acidemia resembles the deep Kussmaul type of hyperventilation seen in diabetic acidosis rather than the usual shallow breathing characteristic of cardiac dyspnea.

PULMONARY CONGESTION AND RIGIDITY AS THE CAUSE OF CARDIAC DYSPNEA

The weight of evidence supports the belief that cardiac dyspnea is due, as a rule, to pulmonary congestion resulting from left-sided heart failure, although measurements of the pulmonary blood volume are equivocal.[13, 11, 8, 11] From the clinical pathologic

viewpoint this concept is supported by the observation that dyspnea is the essential symptom of left sided heart failure and that pulmonary congestion is the essential pathologic feature The pulmonary rigidity may be due to increased pulmonary capillary and venous pressure and interstitial edema as well as possible encroachment of congested pulmonary capillaries on the alveolar spaces

Pulmonary congestion disturbs respiration either (a) by hampering the diffusion of oxygen and thus impairing aeration of the blood or (b) by interfering mechanically with the expansion and retraction of the lungs We have seen that chemical changes in the blood do not appear to account for the usual cardiac dyspnea and therefore any tendency to impairment in aeration is well compensated It remains to discover by what means mechanical disturbances in pulmonary expansion and retraction account for most instances of cardiac dyspnea

The Hering Breuer Reflex

Normal involuntary respiration is dependent on the Hering Breuer reflex in which the changing alveolar tension is the stimulus the vagus nerve is the afferent arc to the respiratory center and the intercostal and phrenic nerves are the efferent pathways to the intercostal and other muscles of respiration including the diaphragm A diminished alveolar tension results in muscular expansion of the chest wall and diaphragm followed by pulmonary expansion due to the increasing negative pleural pressure The high intra alveolar tension at the peak of inspiration causes reflex relaxation of the chest wall and the intrinsic elasticity of the lung causes pulmonary retraction

Pulmonary Congestion and Reflex Stimulation of Respiration

Experimental evidence supports the theory that pulmonary congestion stimulates respiration by way of the Hering Breuer reflex and thus causes the rapid shallow breathing of cardiac dyspnea The production of pulmonary congestion in cats[1] and dogs[47] by pulmonary vein ligation and infusion of blood into the pulmonary artery or by multiple pulmonary embolization[3] [9] caused rapid shallow breathing which disappeared after section of the vagi The altered respiration was unassociated with changes in the chemical composition of the blood If the stimulus to rapid breathing is regarded as distention of the pulmonary alveoli the reflex is termed the Hering Breuer reflex if the stimulus is distention of the pulmonary vessels the reflex is termed the Churchill Cope reflex[11]

Pulmonary Congestion and the Rapid Shallow Respiration of Cardiac Dyspnea

To understand the manner in which pulmonary congestion induces the rapid shallow respiration of cardiac dyspnea it should be recalled (1) that distensibility of the lungs is essential to their easy expansion during inspiration and their elasticity is essential to their retraction during expiration and (2) that the lung like erectile tissue becomes rigid and inelastic when congested with blood[29 30 11] Because of the rigidity of the lungs the normal increase in alveolar tension during inspiration causes relatively less expansion of the alveoli for the same reason there is relatively less retraction during expiration than normally Thus the end points of pulmonary inflation and deflation are brought close together with a consequent shallow respiration

Were there no compensations the shallow respiration would be accompanied by inadequate pulmonary aeration and a resulting accumulation of carbon dioxide and deficiency of oxygen in the blood Since the volume of pulmonary ventilation can be modified only by alteration in respiratory amplitude or in respiratory rate it is apparent that the reduction in respiratory amplitude in congestive heart failure can be neutralized only by a compensatory increase in rate i e by tachypnea Thus compensatory tachypnea accounts for our observation that despite the shallow respiratory excursions of the inelastic congested lung homeostasis of the blood with respect to its oxygen content is long maintained in congestive heart failure

Pathogenesis of Tachypnea in Heart Failure

The exact mechanism by which pulmonary congestion induces tachypnea is uncertain It seems clear that the first consequence of pulmonary congestion and rigidity is a deficiency in ventilation due to (a) a diminution in the quantity of air inspired and exhaled with each breath (b) uneven ventilation because less favorably situated alveoli and those which are most rigid are not expanded at all and (c) impairment of diffusion because of the thickened alveolar septa encroachment of ectatic wide capillaries on the alveolar spaces and transudation of fluid into the alveoli

Initially, these disturbances tend to cause a reduction in oxygen content of the blood The carotid body and respiratory center are chemically stimulated and induce increased respiration Since pulmonary rigidity prevents or limits augmentation in the depth of respiration ventilation is enhanced by an increase in the rate The degree of acceleration and the amount of increase in ventilation appear to be that which suffices to restore the normal oxygen content of the blood

Vagal reflexes from the congested, rigid lung are concerned in the production of compensatory tachypnea, for in experimental pulmonary congestion rapid breathing no longer is induced if the vagi are cut Increased sensitivity of the sensory endings concerned with the Hering Breuer reflex and more frequent stimulation to inspiration and expiration because of the shallow respiratory range may account for the resulting tachypnea Reflex tachypnea has also been attributed to increased pressure in the pulmonary veins and left atrium on the basis of experimental observations [5]

If there were a change only in the *quantity* of each breath during shallow respiration of heart failure then a 30 per cent reduction in amplitude would require a 30 per cent increase in rate to compensate The total amount of ventilation would be unaltered However pulmonary rigidity causes not only a reduction in ventilation but an inefficiency in ventilation and in diffusion aeration of the blood Consequently in the example mentioned a 30 per cent reduction in amplitude might require a 50 per cent compensatory increase in respiratory rate The total quantity *of ventilation per minute is increased*[81] but the effective aeration of the blood is normal Since carbon dioxide diffuses more readily than oxygen the hyperventilation needed to restore the normal oxygen saturation results in an excessive elimination of carbon dioxide

In summary pulmonary congestion causes pulmonary rigidity which restrains inspiration and expiration and results in restricted or shallow breathing An increased respiratory stimulus most probably neurogenic by way of an exaggerated Hering Breuer reflex but also or occasionally chemical (hypoxemia), increases ventilation by increasing the rate and to a limited degree the depth of respiration

Relation of Cardiac Dyspnea to Pulmonary Ventilation and Vital Capacity

It has been mentioned that the shallow rapid respirations of congestive heart failure are associated with an elevated total ventilation [81] Peabody and his associates[94] also demonstrated that the vital capacity is reduced and that there is a close correlation between the degree of reduction and the severity of dyspnea Frank et al [38] discovered a symmetrical reduction in both inspiratory capacity and expiratory reserve, the elements that compose the vital capacity (p 972) Christie and Meakins[20] showed that in patients with congestive heart failure the vital capacity was a gauge of the rigidity of the lungs More recent observations have demonstrated only fair correlations between dyspnea and vital capacity [1, 2, illegible]

The intensity of dyspnea has been correlated not only with the reduction in vital capacity but also with the increase in rate and total ventilation Harrison and his co-workers[49] observed that dyspnea usually occurred when the ratio $\frac{\text{ventilation}}{\text{vital capacity}}$ exceeded a given value More recently an excellent correlation has been found between the occurrence of dyspnea and the ratio of breathing reserve to maximal breathing capacity (p 974) The latter averages 100 liters per minute for normal females and 150 liters per minute for normal males and is determined by having the patient breathe in and out as fast and deeply as possible for 5 to 20 seconds (p 974) The breathing reserve is the maximal capacity minus the actual ordinary minute ventilation in any given state In congestive *heart failure there is both a reduction in* maximal breathing capacity and an increase in actual ventilation, the breathing reserve is diminished by both of these changes Dyspnea has usually been found to occur when the breathing reserve is below 70 or 65 per cent of the maximal breathing capacity

Richards et al [10] found a slight decrease in the expiratory reserve volume and a slight increase in the residual volume and functional residual volume with moderate congestive heart failure In severe heart failure there was a sharp reduction in the residual volume and functional residual volume

This correlation between the severity of dyspnea and quantitative changes in ventilatory function does not denote that the dyspnea

is caused by these changes The increased respiratory rate and diminution in vital capacity and maximal breathing capacity are *consequences* of pulmonary congestion and rigidity just as is the dyspnea These and other quantitative changes in pulmonary respiration are merely indices of the pulmonary rigidity It is the pulmonary congestion and rigidity per se which cause dyspnea This is confirmed by recent pressure flow studies with an intra-esophageal balloon, which revealed an alteration in the mechanics of ventilation caused by changes in the elastic properties of the lung [19, 21]

PATHOGENESIS OF SUBJECTIVE DISTRESS DURING DYSPNEA

The mechanisms discussed above attempt to explain the pathogenesis of the rapid shallow breathing and the objective disturbances in ventilation associated with dyspnea but do not reveal why the patient suffers distress The most probable causes for subjective discomfort are the excessive work of the muscles of respiration and the use of muscles not ordinarily required in unconscious breathing to distend and deflate the rigid lungs The increased intrathoracic pressure resulting from the loss of pulmonary elasticity[20] and the increase in the number of respirations per unit time add to the burden Pulmonary ventilation is limited by the maximal work capacity of the respiratory muscles When the latter cannot readily provide the increased ventilation in heart failure needed to aerate the blood dyspnea results [101] See also Work of Breathing and Respiratory Effort[77, 78] (p 975) The localization of the distress in the upper abdomen, chest wall and neck seems to confirm the impression that the subjective discomfort with dyspnea arises from fatigue of the muscles of the chest wall and of the diaphragm The exaggerated work of the respiratory muscles accounts for most of the increased oxygen consumption in dyspneic patients Various constitutional and psychic conscious and subconscious factors influence the character and degree of discomfort (dyspnea) resulting from this exaggerated work and fatigue of the respiratory muscles

PRODUCTION OF DYSPNEA DURING RIGHT SIDED HEART FAILURE

Dyspnea is usually present in patients with right sided heart failure As a rule it is due to persistence of the pulmonary congestion of left-sided heart failure, since the latter usually precedes right sided heart failure But following failure of the right ventricle the dyspnea may be partially alleviated in proportion to the relief of pulmonary congestion

In some cases right-sided heart failure is secondary to primary pulmonary disease such as extensive emphysema, fibrosis, etc The dyspnea may then be caused entirely by the pulmonary disease and not by failure of the right side of the heart

In addition to the contributions of pre existing pulmonary congestion or of intrinsic pulmonary disease to the production of dyspnea in patients with right heart failure, the latter itself may contribute as follows

1 Severe peripheral venous stasis may cause a significant reduction in the oxygen tension and an increase in the carbon dioxide tension of the venous blood returning to the lungs The combination of pulmonary congestion and severe tissue stasis cannot be adequately compensated and the oxygen saturation of the arterial blood is significantly reduced The resultant hypoxia of the carotid body and respiratory center may contribute to the occurrence of dyspnea

2 Severe venous stasis with right sided heart failure may lead to an increase of lactic acid in the blood This may increase the hydrogen ion concentration of the blood especially in hypertensive patients with renal damage The change in chemical composition of the blood stimulates the respiratory center and may cause hyperventilation and dyspnea

3 Right sided heart failure is associated with a rise of pressure in the venae cavae and right atrium Harrison and his associates[11] found that when they elevated the pressure in the venae cavae by the rapid injection of fluid or by insertion and inflation of a balloon there was an increase in respiration which did not occur if the vagi were sectioned These experiments suggest that an elevation of pressure in the venae cavae and right atrium, such as occurs with right sided heart failure may reflexly stimulate breathing and therefore may contribute to the development of dyspnea However, the occurrence of such reflexes in human beings is questionable

4 Hydrothorax ascites and extreme and sudden hepatic enlargement occurring during right-sided heart failure may precipitate or

accentuate dyspnea, by interfering with the distensibility of the lungs[102]

RELATION OF EFFORT TO CARDIAC DYSPNEA

In its early stages cardiac dyspnea is usually initiated only after certain degrees of exertion which however, did not cause dyspnea before the patient's heart failed Pulmonary congestion with consequent rigidity *of the lungs is the fundamental basis* for cardiac dyspnea whether it appears during rest or after exercise The patient with left sided heart failure experiences pulmonary congestion, even at rest, but it may be insufficient to produce dyspnea During exercise this congestion is further increased until the patient experiences dyspnea Thus very severe pulmonary congestion may cause dyspnea at rest, with lesser degrees of congestion dyspnea only occurs when pulmonary congestion is intensified to the symptom level by exercise or other means

Exercise increases pulmonary congestion by augmenting the venous return[71] If the right heart is competent this augmented return is effectively expelled into the already congested lung while the weak left heart is unable to drain effectively the pulmonary venous return For this reason pulmonary congestion and dyspnea are usually most intense when failure is limited to the left heart In patients with left-sided failure due to mitral stenosis exercise *resulted in a rise in pulmonary capillary* pressure and a reduction in pulmonary compliance[103] If the increased congestion is associated with a high enough pulmonary capillary pressure pulmonary edema occurs and intensifies the dyspnea Psychic stimulation of respiration, increased production of lactic acid reflexes from the muscles[**] and reflexes stimulated by an increase in venous pressure have also been suggested as factors in the dyspnea induced by exercise[43]

PATHOGENESIS OF ORTHOPNEA

Since essentially the same factors are concerned in the pathogenesis of orthopnea as of any other form of dyspnea we will consider only the role of the recumbent position in the promotion of dyspnea Again it must be emphasized that, like dyspnea cardiac orthopnea is a cardinal symptom of left sided heart failure and is due fundamentally to pulmonary congestion Furthermore when the right side of the heart fails and pulmonary congestion is relieved orthopnea is often alleviated despite the elevation of venous pressure peripheral tissue stasis and other related phenomena

1 Increased Pulmonary Congestion in Recumbent Position

There is considerable evidence that there is a shift of blood from the upper half of the body to the splanchnic area and lower extremities with assumption of the erect position and the reverse with recumbency[33] This gravitational shift of blood is noted clinically in the altered degree of filling of the superficial veins of the extremities and was demonstrated plethysmographically by Atzler and Herbst[6] The circulating blood volume is increased in the recumbent position[1, 4, 95] It may be presumed that in the recumbent position the shift of blood to the thorax from the lower extremities and splanchnic viscera increases pulmonary congestion Most significant are the observations that the cardiac output and therefore the venous return are augmented when an individual changes from an upright to a recumbent position[83] In the presence of left-sided failure such an increase in venous return intensifies pulmonary congestion as explained under the effect of exercise

Confirmation of increased pulmonary congestion in the recumbent position is offered by comparative measurements of vital capacity *when patients with orthopnea are* erect and supine Christie and Beams[19] found that while the vital capacity in normal persons was diminished 5 per cent by a shift to the horizontal position there was an average fall of 25 per cent in patients with orthopnea This observation has been confirmed by others including Calhoun and his co-workers[17] Since the diminution in vital capacity is a measure of the degree of pulmonary congestion and rigidity of the lung these changes in vital capacity indicate an increase in pulmonary congestion with assumption of a horizontal position More recently Marshall et al[77] determined that in patients with orthopnea due to mitral stenosis and left-sided heart failure there was an increase in elastic resistance (diminished compliance) on lying flat and a marked increase in respiratory work This was associated with diminished tidal volume increased respiratory rate and dyspnea Adoption of the recumbent position by increasing the pulmon

ary congestion and rigidity already present in patients with heart failure either initiates or intensifies dyspnea by mechanisms already discussed

2 Mechanical Interference with Pulmonary Ventilation in Recumbent Position

When the patient with cardiac orthopnea reclines the diaphragm is elevated and consequently interferes with thoracic breathing by shortening the thoracic compartment available for expansion[8] The mechanical factor is especially important in the presence of cardiac ascites enlarged liver and abdominal tympanites which not only elevate the diaphragm but also interfere with diaphragmatic breathing Even in normal subjects changing from the upright to the recumbent position diminishes the expiratory reserve (p 972) probably due to elevation of the diaphragm[10]

PATHOGENESIS OF PAROXYSMAL DYSPNEA AND CARDIAC ASTHMA

Relation to Pulmonary Congestion[72]

This discussion is concerned with the paroxysmal attacks of dyspnea which as a rule occur at night and wake the patient from sleep As indicated by Hope[11] who first employed the term cardiac asthma pulmonary congestion is the fundamental basis of these attacks as it is for dyspnea at rest or on exertion That cardiac asthma results from pulmonary congestion is indicated by its occurrence almost exclusively in patients with hypertensive aortic or mitral valvular or coronary artery disease or other conditions which are complicated by left sided heart failure Circulatory studies on patients between attacks of cardiac asthma also show that they are suffering from pulmonary congestion Weiss and Robb[1 8] found that there was an increase in the volume of blood in the lungs a retardation of the pulmonary blood flow and a reduction in vital capacity On the other hand the systemic circulation is unchanged since the stroke and minute volume the velocity of peripheral blood flow the arteriovenous difference and the systemic venous pressure are all normal in the great majority of cases Furthermore the observations of Weiss and Robb[1 6] and of Calhoun et al[17] have shown that neither a diminished blood flow to the respiratory center nor changes in blood gases can account for cardiac asthma

Clinical and circulatory observations reveal that *during* the attacks of cardiac asthma the severity of pulmonary congestion is increased Pulmonary râles appear or become more extensive The second pulmonic sound becomes more accentuated and may be louder than the second aortic sound even when hypertension is present The low vital capacity is further diminished during the attacks The velocity of blood flow in the lungs is diminished and there is an increase in the volume of the pulmonary vascular bed indicating an intensification of pulmonary engorgement[1 6]

The actual precipitation of an attack of cardiac asthma is due to some factor or factors which intensify the preexisting pulmonary congestion sufficiently to cause clinical dyspnea Such factors usually intensify pulmonary congestion by enhancing the venous return[11] In addition variations in the sensitivity of the respiratory center e g during sleep are also concerned both in the initiation and subsidence of an attack of cardiac asthma

Mechanism of Precipitating Factors in Paroxysmal Dyspnea or Cardiac Asthma

Recumbency Often the patient suffers from orthopnea while awake and therefore goes to sleep while propped up on pillows The attack of dyspnea is precipitated when he slides down during sleep to a more horizontal position The significance of this factor is confirmed by the frequency and rapidity with which an attack is relieved as soon as the patient sits up or gets out of bed to go to a window The mechanisms involved were discussed under orthopnea The main factor is a redistribution of blood which increases the return to the right side of the heart and lungs

Sleep A characteristic feature of cardiac asthma is its occurrence after patients fall asleep It has been assumed that the diminished irritability of the central nervous system when the patient is asleep permits the lungs to become much more engorged as a result of recumbency than when he is awake When the patient is awake reflex hyperventilation and slight dyspnea appear before pulmonary congestion is intense and the patient consciously or unconsciously assumes a somewhat oblique if not completely vertical position During sleep however the degree of congestion may become so great as to be associated with bronchial spasm edema and

transudation into the alveolar spaces Then the resumption of the erect position may not be adequate to stop the attack immediately An increase in pulmonary blood flow, noted during sleep, may also increase pulmonary congestion [46]

Cough In my experience cough is usually manifested after the attack has already begun and is not a precipitating factor

Terrifying dreams during sleep have been said to precipitate an attack, perhaps by causing an elevation in blood pressure This factor cannot be evaluated Furthermore nightmares occur frequently in cardiac patients who do not experience nocturnal dyspnea

Diminished Muscular Activity Christie[18] has suggested that diminution of muscular activity during sleep causes venous stagnation within the muscles The attacks may then be precipitated by *sudden muscular movement* with a consequent increase in venous return

Increased Blood Volume An increased blood volume due to the resorption of latent edema from the dependent portions of the body when the patient becomes recumbent at night may be an important cause of paroxysmal dyspnea according to Brunn[15] and others [95] This would have the effect of increasing the venous return and thereby the degree of pulmonary congestion The fact that the attacks may be diminished or prevented by a low sodium intake and vigorous diuresis supports the belief that an augmented blood volume is important in the underlying pulmonary congestion

Cardiac asthma is a term applied to those attacks of nocturnal dyspnea which are characterized by wheezing respirations and audible rhonchi in the chest

The exact mechanism responsible for the wheezing resembling that of bronchial asthma, is uncertain but bronchial obstruction is presumed to be the cause This may be due to congestion and edema of the bronchial mucosa, to actual edema fluid in the bronchial lumen or to bronchoconstriction [97] It is uncertain whether this asthmatic dyspnea is due to vagal reflexes from the congested lung to the affected bronchi,[illegible] to congestion and increased hydrostatic pressure in the bronchial capillaries or whether it appears when intense pulmonary congestion occurs in predisposed allergic persons [114]

PATHOGENESIS OF ACUTE PULMONARY EDEMA

Attacks of acute pulmonary edema are essentially severe episodes of paroxysmal dyspnea which are due to the same fundamental factor of sudden intensification of the pulmonary congestion of left sided heart failure This concept is supported by the frequent occurrence of pulmonary edema in the same patients as suffer from cardiac asthma its development under similar circumstances (except that it occurs at any time of the day and not necessarily after retiring), and the common transition of an attack of cardiac asthma into one of pulmonary edema

The essential feature of acute pulmonary edema is the rapid transudation of fluid out of the pulmonary capillaries into the alveoli, beyond the capacity of the pulmonary lymphatics to resorb this fluid [illegible] Elevation of pulmonary capillary hydrostatic pressure and increased capillary permeability are the major factors responsible for pulmonary edema, but reduction in plasma proteins or impairment of function or elevation of pressure in the lymphatics may be contributory [illegible, 90, illegible] Sodium and water retention are important insofar as they contribute to or maintain the elevated pulmonary venocapillary pressure In congestive heart failure acute elevation of the pulmonary capillary pressure appears to be the major causative factor It is probable that a critical level of about 35 to 40 mm of water must be exceeded i e, above the plasma oncotic pressure [illegible, 70] Capillary permeability if altered at all tends to be diminished owing to fibrosis and thickening of the capillary basement membrane and alveolar capillary membrane as in mitral stenosis Such impairment of permeability may account for imperfect correlations between the height of the pulmonary capillary pressure and the presence or absence of pulmonary edema [4] Acute pulmonary edema occurs in those cardiac diseases which are complicated by left ventricular or left atrial failure in which there is a continuous pulmonary congestion and elevation of pulmonary capillary pressure The actual onset of acute pulmonary edema is triggered by a marked increase in resistance to outflow from the left cardiac chambers a sudden reduction in left ventricular or left atrial output an excessive rapid increase in venous return and

right ventricular output or a combination of these, which swiftly raise further the elevated pulmonary capillary pressure above the critical edema level

The precipitation of pulmonary edema by intravenous infusions of saline or plasma or by transfusions of blood and its occurrence in mitral stenosis after strenuous exertion, during pregnancy or post partum or after excessive sodium intake, supports the theory that pulmonary edema like cardiac asthma may be elicited by a sudden augmentation of the venous return and intensification of pulmonary congestion and capillary hypertension Conversely acute pulmonary edema is often relieved by venesection or the application of tourniquets to the extremities—factors which reduce the venous return and the pulmonary capillary pressure Experimentally Welch[121] long ago demonstrated in rabbits that pulmonary edema could be produced by compression of the left ventricle or aorta and by ligation of most of the pulmonary veins procedures which diminished the left ventricular output and caused intense pulmonary congestion and elevation of pulmonary capillary pressure Attacks of pulmonary edema in hypertensive patients are precipitated by sudden increases in blood pressure (i e in peripheral resistance)[54] at the same time that resorption of edema fluid increases the venous return when such patients have been recumbent during the night Marked elevation of pulmonary capillary pressure and pulmonary edema occur in acute myocardial infarction as a result of severe left ventricular damage and diminished output In mitral stenosis further elevation of pulmonary capillary pressure and pulmonary edema may occur when the tachycardia exercise or other factors increase the cardiac output[44] (p 654) Because of the unyielding resistance of the narrow mitral orifice the increased blood flow is translated into increased pulmonary venous and capillary pressure There is evidence that acute pulmonary edema occurs not as a rule in the most advanced cases of mitral stenosis but in moderately severe cases in which the cardiac output can be increased with exercise[34, 45, 1.5]

The chief difference between pulmonary edema and cardiac asthma is the occurrence in the former of a much more extensive exudation of edema fluid around the alveolar septal vessels within the alveoli, in the bronchial walls and in their lumina The edema results from a pronounced increase of the hydrostatic pressure in the pulmonary capillaries due to the intensification of pulmonary venous engorgement The relatively high protein content (2 to 4 per cent) in pulmonary edema fluid suggests that increased permeability of the vessel walls facilitates the formation of pulmonary edema, according to Drinker[27]

Other Theories of Pulmonary Edema[74, 2]

Pulmonary edema is not invariably due to left-sided heart failure It may occur (a) in pneumonia and in poisoning with certain war gases (phosgene) and especially (b) in certain diseases of the brain such as trauma, tumors, hemorrhage and encephalitis In the former group local damage to pulmonary capillaries may predispose to edema by increasing capillary permeability, its occurrence in the latter suggests a neurogenic mechanism which could likewise promote permeability But Paine and associates[92] found that even in the group of patients with serious disease of the central nervous system in whom pulmonary edema developed the majority showed evidence of heart disease at autopsy or had hypertension during life Neurologic disease may induce pulmonary edema not by increasing capillary permeability but by adding the stress of neurogenic hypertension, anoxia and cardiac arrhythmia to underlying cardiac disease

The pulmonary edema of clinical left ventricular or left atrial failure has also been attributed to neurogenic reflexes arising in the root of the aorta, the carotid receptors the pulmonary artery and large veins and in the left ventricle[119, 74] Wassermann[119] described observations on patients whose attacks of paroxysmal dyspnea were relieved by section of the depressor nerves and by pressure over the carotid sinus

There is convincing evidence favoring sudden intensification and critical elevation of pulmonary capillary pressure as the fundamental cause of the pulmonary edema in clinical cases of left sided heart failure The efficacy of a reduction in blood volume and venous return by sodium restriction mercurial diuresis venesection or the application of tourniquets in preventing and controlling pulmonary edema has been mentioned However, the prompt therapeutic effectiveness of morphine in many cases is noteworthy and

suggests some causative role of the nervous system in the production of cardiac asthma and pulmonary edema But special aortic carotid, ventricular or other vascular reflexes need not be postulated The theory of pulmonary congestion as the basis of pulmonary edema has necessarily included the sensitivity of the respiratory center in mediating the efferent neural arc which effects increased respiratory rate and ventilation Since the compensatory tachypnea must be mediated through the respiratory center, morphine provides relief by depressing the sensitivity of this center to the stimuli which induce increased respiratory ventilation The frequently marked and rapid relief of cardiac asthma or pulmonary edema by morphine is largely due to its diminution of the work of respiration by reducing the quantity of ventilation Anxiety also is allayed There is no direct evidence that it corrects the basic cause or mechanisms of pulmonary edema

The pathogenesis of acute pulmonary edema occurring in conditions other than left heart failure may be unrelated to pulmonary congestion e g toxic or neurogenic increase in capillary permeability [27]

PATHOGENESIS OF CHEYNE STOKES RESPIRATION

Two factors are concerned in the development of Cheyne-Stokes respiration (1) a diminished sensitivity of the respiratory center and (2) a relatively inadequate concentration of carbon dioxide to stimulate the respiratory center

Diminished Sensitivity of Respiratory Center

Cheyne-Stokes respiration is not a specific feature of congestive heart failure It is seen most frequently in patients with cerebral tumors and other cerebral lesions and in elderly patients with cerebral atherosclerosis who receive morphine or other strong cerebral depressants factors which may diminish the sensitivity of the respiratory center Congestive heart failure itself is associated with diminished sensitivity of the respiratory center [110] Sleep is a predisposing factor because it is associated with a diminished sensitivity of the respiratory center The relief of Cheyne-Stokes respiration by aminophylline is probably due to direct or indirect stimulation of the respiratory center The cerebral blood flow is diminished by aminophylline, this may result in increased carbon dioxide tension in the respiratory center [111]

Inadequate Respiratory Stimulus (Acapnia)

With *severe* depression of the respiratory center even a normal content of carbon dioxide in the blood may be insufficient to stimulate the center, following temporary apnea periodic breathing may be induced With lesser degrees of medullary depression Cheyne-Stokes respiration is precipitated only if there is a reduction in the carbon dioxide tension i e, if there is a diminution in the normal respiratory stimulus In cases of congestive heart failure with dyspnea overventilation results in an excessive pulmonary elimination of carbon dioxide and consequent reduction in its arterial concentration (acapnia) When diminished responsiveness of the respiratory center (due to sleep morphine, cerebral arteriosclerosis) is combined with a deficient respiratory stimulus (due to hyperventilation in left sided heart failure) a period of apnea is produced and periodic breathing follows

The Cycle of Cheyne Stokes Respiration

The subsequent waxing and waning of periodic respiration is explained as follows During the initial apnea there is a progressive reduction in arterial oxygen saturation, Arterial hypoxemia stimulates the carotid sinus and thereby the respiratory center to resume respiration At the same time an increase in carbon dioxide tension during the apneic phase directly stimulates the respiratory center This sudden and exaggerated stimulation of the respiratory center by both hypoxemia and excess of carbon dioxide results *in an overshooting of the crescendo phase of* respiration, with resulting hyperpnea This exaggerated hyperpnea again excessively reduces the carbon dioxide content of the blood and is followed by waning respiration apnea and a repetition of the cycle

The importance of the carbon dioxide content of the blood in the pathogenesis of Cheyne-Stokes respiration is indicated by the following observations Cheyne-Stokes respiration can be induced by voluntary overventilation which reduces the blood carbon dioxide tension [5], overventilation in an atmosphere containing 5 per cent carbon dioxide fails to cause this type of periodic breathing, the administration of carbon dioxide abolishes Cheyne-Stokes respiration [3] the carbon di

oxide tension of arterial blood is reduced in patients with Cheyne-Stokes respiration [50]

Arterial Hypoxemia

Arterial hypoxemia does not initiate the attack [42] for the oxygen saturation is normal in patients with heart failure who are subject to Cheyne-Stokes respiration and the administration of oxygen does not abolish the attack [4] But arterial hypoxemia is important in causing the crescendo phase after apnea has been initiated by a reduction in carbon dioxide in a patient with a hyposensitive respiratory center Oxygen given during Cheyne-Stokes breathing only modifies it by prolonging the apnea and making the hyperpnea less stormy [116] For the anoxic stimulus to overventilation is removed and the latter is produced only by the excessive carbon dioxide which accumulates during apnea

Cheyne Stokes Respiration and the Adams Stokes Syndrome

Cheyne-Stokes breathing sometimes occurs in connection with the Adams-Stokes syndrome in complete heart block During the prolonged period of cardiac arrest cerebral ischemia depresses respiratory irritability At the same time the arterial hypoxemia which develops during circulatory standstill results in hyperventilation and excessive elimination of carbon dioxide When the heart resumes beating the respiratory center is relatively insensitive and the blood which is propelled to it is deficient in carbon dioxide These are the factors initiating the apnea of Cheyne-Stokes respiration Hyperpnea and dyspnea occur during cardiac standstill and apnea during resumption of cardiac contraction

PATHOGENESIS OF CARDIAC EDEMA

Sodium Water Retention

Cardiac edema has long been attributed primarily to an increased venous pressure and consequently to an elevated hydrostatic pressure within the capillaries [115, 77] In recent years emphasis has shifted to the importance of sodium and water retention within the body for without it generalized edema cannot occur It is apparent from the rapid large increase in weight with the development of edema and the similar loss of weight with disappearance of edema that edema formation depends on a positive external fluid balance

Transudation of the normal quantity of plasma fluid from the capillaries into the interstitial fluid cannot possibly account for the vast quantity of edema fluid which often equals many times the total quantity of plasma (p 168) Therefore capillary transudation of plasma filtrate can continue to form such quantities of edema fluid only if the plasma is continually replaced by concomitant renal retention of fluid

The discovery that in congestive heart failure there is an impaired renal excretion of sodium (p 169) has called attention to the importance of the kidney in the edema of heart failure (p 171) The therapeutic efficacy of extreme reductions in sodium intake and likewise of mercurial diuretics which produce a notable increase in sodium excretion has reinforced the belief that sodium balance is the cardinal factor in the production and disappearance of edema Similarly the production of edema in patients with Addison s disease by excessive dosage of desoxycorticosterone and sodium (p 173) stresses the importance of both sodium and renal function because desoxycorticosterone promotes renal tubular reabsorption of sodium

The possible manner in which cardiac failure impairs the renal excretion of sodium and water and leads to edema has been discussed in detail (p 171) In the same chapter the relative importance of sodium water retention and of elevated venous pressure in the pathogenesis of cardiac edema was considered In brief it was concluded that sodium water retention is a prerequisite for the development of edema but edema is not necessarily a *direct* consequence of salt-water retention Hypervolemia increased venous return to an incompetent cardiac chamber and increased venous and capillary pressure are a sequence of events which determine the appearance and localization of edema after renal retention of sodium and water occur According to the Starling theory an increased venous and capillary pressure first induces transudation of plasma fluid and reduction of plasma volume which somehow then lead to retention of sodium and water and edema formation

Increased Venous Pressure

The studies of Starling[115] showed that a passage of fluid from the capillaries into the tissues occurred when the hydrostatic pressure within the capillaries exceeded the colloid osmotic pressure of the serum protein Thus the accumulation of fluid in the tissues may be due either to an elevation of capillary hydrostatic pressure or to a diminution of

serum proteins or both Normally there is a gradual fall of pressure as the blood passes from the arterial limb to the venous limb of the capillaries and thence to the great veins According to the direct microscopic studies of Landis [67] the pressure in the arterial limb of the human capillary is about 42 cm of water and in the venous limb about 16 cm of water Since the colloid osmotic pressure is about 30 cm of water the equilibrium between the two factors is normally such as to cause fluid transudation into the tissues at the arterial limb and fluid resorption at the venous limb

The normal pressure in a medium sized subcutaneous vein is about 4 to 8 cm of water In cases of heart failure associated with subcutaneous edema the venous pressure commonly rises to between 15 and 25 cm of water and sometimes higher According to the studies of Fahr and Ershler,[37] who used Landis' method for measuring capillary pressure edema tends to develop when the hydrostatic pressure in the venous end of the capillary is 26 cm of water which corresponds to a pressure in the arm vein of 17 cm of water There is a corresponding rise in the hydrostatic pressure of the capillaries so that it greatly exceeds the colloid osmotic pressure of the blood in the venous as well as the arterial limb The result is a transudation of fluid into the tissue spaces with consequent edema

The belief that edema forms because of increased venous (and therefore capillary) hydrostatic pressure is based on considerable experimental and clinical evidence [106] Venous ligation in animals and humans, which causes a local rise in venous pressure, has resulted in edema of the affected subcutaneous tissues [21] Landis[67] showed that when the hydrostatic pressure in the capillaries of the frog s mesentery exceeded the colloid osmotic pressure of the blood there was a transudation of fluid out of the capillaries Quantitative plethysmographic studies on humans by Krogh Landis and Turner[63] revealed that after compression of an extremity fluid accumulated in the tissue spaces when the venous pressure exceeded 15 to 20 cm of water, a pressure similar to that seen frequently in patients with right sided heart failure

The importance of an elevated venous pressure in causing cardiac edema is demonstrated clinically by the frequency of edema in patients with right sided heart failure, in whom the elevated venous pressure is a characteristic feature and by the absence of subcutaneous edema in patients with left-sided heart failure whose systemic venous pressure is normal On the other hand, pulmonary edema occurs frequently in cases of isolated left sided heart failure in which an elevation of the venocapillary pressure is limited to the pulmonary circulation That a diminished blood supply to the tissues is not a causative factor appears clear from the absence of edema in patients with shock due to acute circulatory failure The greater frequency and intensity of cardiac edema in the lower extremities of ambulant patients may also be explained by the higher venous and capillary pressure due to gravity In normal subjects the average venous pressure in the lower extremities was found to be 12 cm water in recumbency 56 cm in the sitting and 86 cm in the standing position and 23 cm during walking [98]

The essential causal relationship of an elevated venous pressure to cardiac edema has been questioned particularly by those who oppose the backward failure hypothesis Altschule[1] emphasized that while in general there is a correlation between increased venous pressure and the presence of edema there is considerable overlapping of the values of venous pressure in edematous and non edematous patients In many edematous patients the venous pressure was no higher than in patients without edema Only when the venous pressure rises as high as 30 to 40 cm of water does Altschule believe it may be considered solely responsible for the formation of cardiac edema One possible explanation for these discrepancies is the variation in venous pressure according to the patient s activity [81] Isolated measurements of venous pressure made with the patient at rest do not reflect these variations Shifts in edema fluid occur much more slowly than changes in venous pressure dependent on rest and exercise Variations in sodium intake tissue pressure and other secondary factors may also account for incomplete correlations between degree of elevation of venous pressure and of edema

Despite any objections increased capillary hydrostatic pressure together with increased sodium water retention appears to be a major factor in the pathogenesis of cardiac edema Sodium water retention without ele

vation of venous pressure causes edema only in exceptional circumstances Conversely when sodium water retention is markedly inhibited by severe restriction of sodium intake increased capillary hydrostatic pressure can only cause a limited transfer of plasma fluid to interstitial fluid and only a limited degree of edema Increased venous (or capillary) pressure may also indirectly influence the formation of edema by actually stimulating the renal retention of sodium and water (p 171)

Reduction in Colloid Osmotic Pressure

Normally the force of hydrostatic pressure which tends to cause an escape of fluid from the capillaries is counterbalanced by the colloid osmotic pressure of the blood proteins which tends to draw fluids from the intercellular tissue into the capillaries The colloid osmotic pressure develops because the blood is separated from the intercellular tissue fluids by a membrane (the capillary wall) which is relatively impermeable to protein The plasma albumin is most important in producing osmotic pressure because its concentration is greater than that of the globulin and because its molecule is smaller The normal colloid osmotic pressure is between 30 and 34 cm of water which is about equal to the average hydrostatic capillary pressure less than the capillary pressure at the arterial end and more than the venocapillary pressure

A sharp reduction in blood proteins especially in plasma albumin and the resulting diminution in osmotic pressure may permit the unbalanced hydrostatic capillary pressure to cause an escape of fluid into the tissues Subcutaneous edema has been produced experimentally in animals by plasmapheresis [7] The edema associated with certain nephrotic states and with starvation has been attributed to the very low blood proteins in these conditions But there is often a lack of correlation between the severity of the edema and the diminution in proteins the edema may disappear while the proteins are still low

In cases of congestive heart failure there is often a reduction in the concentration of plasma protein especially of the important albumin fraction [104, 82] In general the reduction in blood proteins in most cases of heart failure is relatively small but occasionally it is pronounced as in cases of constrictive pericarditis A corresponding diminution in the colloid osmotic pressure was demonstrated by the direct measurements of Iversen and Nakazawa [86]

According to Payne and Peters [91] the reduction in plasma proteins is caused chiefly by malnutrition due to anorexia low protein intake and vomiting Pronounced passive congestion of the intestinal mucosa may somewhat impair the absorption of amino acids Prolonged loss of small amounts of albumin in the urine and in pleural and peritoneal exudates may also decrease serum albumin Increase in plasma volume may diminish the concentration of albumin Finally longstanding congestion and anoxemia of the liver may impair its ability to elaborate serum protein but Bauman et al [8] in measurements of exchangeable albumin by means of I^{131} labeled albumin found no significant alteration in albumin synthesis by patients with congestive heart failure A reduction in serum proteins does not in itself cause edema unless the concentration falls below 5 gm per 100 cc (albumin below 2 5 gm per 100 cc) Therefore the lesser degrees of hypoproteinemia often seen in patients with congestive heart failure are usually insufficient to produce edema and at most represent a minor accessory causative factor But when hypoproteinemia is pronounced correction of this factor may be important in controlling edema

The colloid osmotic pressure of serum protein is somewhat neutralized by the osmotic pressure of the protein in tissue fluid However the protein content of the latter is much less (about 0 5 per cent) than that of serum protein and its osmotic pressure is only about 3 cm of water as compared to 30 cm for the colloid osmotic pressure of the blood The effective colloid osmotic pressure tending to draw fluid into the capillaries would be 27 cm of water Occasionally the protein content of tissue fluid is greatly increased e g when there is lymphatic obstruction because the lymphatics serve to return protein from the tissue spaces to the veins [80] Under such circumstances edema formation is greatly facilitated because the effective colloid osmotic pressure in the blood is reduced by the high colloid osmotic pressure of tissue fluid However this factor is not important in the edema of congestive heart failure

Tissue Pressure

The extracapillary tissues themselves exert a force which resists their distention by fluid

This force is known as tissue pressure It partially counteracts the capillary hydrostatic pressure and thus resists the formation of edema[88, 170] Normally this measures about 3 or 4 cm of water and is greater in the lower extremity than in the upper[103] Low tissue pressure in certain sites such as in the loose tissue of the eyelids promotes the accumulation of fluid there A reduction of tissue pressure in cachectic and bedridden patients with lax subcutaneous tissues and in those whose tissues have been stretched by previous episodes of edema predisposes to the accumulation of edema Such a reduction in tissue pressure probably exists in inactive or bedridden cardiac patients but at most it is an accessory factor in the development of cardiac edema It may however, partly account for some of the imperfect correlations between elevated venocapillary pressure and edema formation

Lymphatic Drainage

Normally the lymphatics are concerned in the removal of tissue fluid and especially of the tissue proteins which have seeped through the capillary wall In patients with cardiac edema this lymphatic flow is impaired due perhaps to the elevated venous pressure which prevents lymphatic emptying into venous channels[80] It is uncertain whether this is of much importance in cardiac edema because the protein content of cardiac edema fluid is low whereas edema fluid caused by lymphatic obstruction contains a high concentration of protein

Capillary Permeability

An increased capillary permeability can be an important factor in producing edema because it permits the escape of proteins with a consequent diminution in the colloid osmotic pressure of the blood and an increase in the colloid osmotic pressure of the tissues Its importance as a factor in cardiac edema has been variously evaluated Ordinarily permeability of a membrane refers to the size of the particles which diffuse through it The capillaries normally permit free diffusion of salts and water but are relatively impermeable to plasma proteins and lipoproteins Therefore minimal quantities of the latter are found in interstitial tissue whereas the various cations and anions appear in concentrations which are determined by Donnan s equilibrium and therefore differ only very slightly from their concentrations in plasma Increased capillary permeability should therefore indicate the diffusion of more than normal quantities of protein and lipoproteins into the interstitial fluid By this definition, as we shall see in the next paragraph, there is no evidence of significant increase in capillary permeability in heart failure On the other hand, Smirk[13] adduced some evidence suggesting an 'increased capillary permeability' to salts and water in heart failure He experimentally elevated the venous pressures of normal persons and of persons with cardiac failure to levels equally in excess of the measured colloid osmotic pressure Despite the same pressure difference he observed a greater accumulation of edema fluid in the cardiac patients He concluded that the capillaries of patients with cardiac failure were more permeable than those of normal persons Burch Reaser and Cronvich,[16] in studies following the intravenous injection of Na^{24} discovered not only an amazing rapid diffusion of sodium through the capillary wall but also that this rate of diffusion was twice as rapid in patients with heart failure as in normal subjects But this increase in diffusion of sodium is not to be construed as an increase in capillary permeability, it can more readily be explained by increased hydrostatic pressure and other factors in cardiac edema already enumerated

The presence of increased capillary permeability in heart failure is suggested by the experiments of Landis[86] who found that capillaries are rendered permeable to protein when deprived of oxygen for three minutes Anoxemia of the capillaries with right sided heart failure is assumed to result from prolonged peripheral stasis Increased permeability in anoxemic capillaries may also be due to vasodilatation with consequent augmentation of the filtering surface Despite these experimental studies and theoretical considerations clinical observations indicate that the factor of increased capillary permeability is not significant in causing cardiac edema In many patients with cardiac edema the oxygen saturation of the blood is normal or only slightly reduced Conversely there is usually no edema in cyanotic patients with congenital heart disease or advanced emphysema despite a low oxygen saturation The degree of anoxia represented by Landis[86] experiments is rarely attained in congestive heart failure The most important objection to the theory of capillary permeability is the low content of

protein (0 2 to 0 5 per cent) in edema fluid [118] Nor is there any change before or after compensation This indicates that there is relatively little increase in capillary permeability an increase which is of only secondary importance in causing cardiac subcutaneous edema On the other hand, varying degrees of permeability in different regions of the body may account for the predominant distributions of capillary transudations e g , the relative intensities of subcutaneous edema and ascites

Hormones

It is known that the pituitary antidiuretic hormone is important in controlling water balance, but little is known of any possible relation to cardiac edema (p 174) The anterior pituitary and adrenal cortical hormones have also been implicated in the production of cardiac edema by their influence on renal retention of sodium The production of edema by the administration of desoxycorticosterone and salt to patients with Addison s disease has been noted The possible role of the adrenal cortical hormone in the renal retention of sodium in patients with heart failure has been discussed (p 173)

PATHOGENESIS OF CARDIAC HYDROTHORAX

The accumulation of fluid in the pleural cavities (hydrothorax) in the course of congestive heart failure is due to the same factors which cause subcutaneous edema The factor of increased capillary permeability is relatively more important in the development of hydrothorax than as a cause of anasarca as seen from the higher content of protein in the pleural fluid (2 to 3 per cent instead of 0 2 to 0 5 per cent) Despite the greater permeability of the pleural capillaries hydrothorax occurs less commonly than subcutaneous edema probably because the pleural vessels drain into both the systemic circulation (by way of the azygos veins and the superior vena cava) and into the pulmonary circulation (by way of the pulmonary veins) Thus any tendency to elevation of the pressure within the pleural capillaries because of an elevated venous pressure in one of the circulations (isolated right-sided or isolated left sided heart failure) is compensated by a free drainage into the other system Hydrothorax is most often seen in cases of combined right- and left sided heart failure in which there is back pressure in the pleural capillaries due to venous engorgement in both circulations

There is no generally accepted nor completely satisfactory explanation for the occurrence of hydrothorax more frequently on the right side than on the left The classic explanation held that with enlargement of the right side of the heart the vena azygos major was compressed against the root of the right lung But the anatomic studies of Fetterolf and Landis[23] indicated that such compression is extremely unlikely These observers believed that left-sided effusions result from compression of the left pulmonary veins by a large left atrium and right sided effusions from compression of the right pulmonary veins by a large right atrium

PATHOGENESIS OF ASCITES

Ascites like the transudate in the pleural cavities, is due *fundamentally to the increased* venous pressure which accompanies right-sided heart failure Here too however increased permeability is relatively more important than in the formation of edema because as Salvesen and Linder[104] have shown the ascitic fluid contains 2 to 3 per cent of protein as compared with less than 0 5 per cent in edema fluid Despite this ascites occurs less often than subcutaneous edema and later in the course of congestive heart failure

The greater permeability of the peritoneal capillaries is usually more than offset by the higher pressure in the subcutaneous capillaries, especially in the lower extremities Since patients with cardiac edema often move about while in the early stages of right sided heart failure the factor of gravity causes a greater elevation of venous pressure in the tissues of the lower extremities than in the venules of the peritoneum Even later when the patient sits in a chair or at the side of his bed or propped up in bed because of orthopnea there is a relatively greater capillary hydrostatic pressure in the lower extremities than in the peritoneum

Ascites appears to be more closely related to increase in hepatic capillary pressure and increased permeability of these vessels than to increased hydrostatic pressure and permeability of other peritoneal vessels The high protein composition of ascitic fluid is virtually identical with that of hepatic lymph

Ascites is especially prominent and often

occurs earlier than overt subcutaneous edema in heart failure associated with constrictive pericarditis or tricuspid stenosis In these cases hepatic congestion is especially intense and cardiac cirrhosis not uncommon These observations suggest that the relative degree of hypertension of the hepatic capillaries is a determining factor in the occurrence and prominence of ascites There is evidence that neither portal vein ligation with portal hypertension nor inferior vena caval ligation caudad to the liver is followed by ascites, but that the latter may be induced by inferior vena caval ligation above the level of the liver or by hepatic vein ligation [78, 117]

Other factors are important or contribute to the development or maintenance of ascites Abnormal sodium and water retention by the kidney is essential Marked restriction of sodium intake and the administration of mercurial diuretics greatly limit or prevent the recurrence of ascites The loss of protein in ascitic fluid reduces the plasma albumin and the colloid osmotic pressure thus accentuating the effect of the increased capillary hydrostatic pressure Disturbances in lymphatic flow and hormonal factors may also contribute to the formation of ascites

PATHOGENESIS OF CYANOSIS

The blue coloration of the skin which cyanosis signifies is due to the reduced hemoglobin of the blood The intensity of cyanosis depends on (1) the amount of reduced hemoglobin in the blood and (2) the amount of blood visible in the superficial vessels of the skin

THE AMOUNT OF REDUCED HEMOGLOBIN IN THE BLOOD

The studies of Lundsgaard and Van Slyke[75] revealed that cyanosis usually appears when the amount of reduced hemoglobin in the blood exceeds 5 gm per 100 cc The concentration of reduced hemoglobin in the blood depends on the total amount of hemoglobin in the blood and the percentage of the latter which is uncombined with oxygen

Total Hemoglobin Content

Normally there are about 15 gm of hemoglobin per 100 cc of blood Cyanosis occurs if one third or more of this is uncombined with oxygen (5 gm or more per 100 cc of reduced hemoglobin), i e, if there is less than 66⅔ per cent oxygen saturation of the blood in the superficial vessels of the skin In patients with polycythemia, whose total hemoglobin is 20 gm per 100 cc, cyanosis would appear even if the oxygen saturation were 75 per cent (25 per cent unsaturation of 20 gm = 5 gm reduced hemoglobin) On the other hand extreme oxygen unsaturation is necessary to produce cyanosis in anemic patients If the total hemoglobin content is less than 33 per cent of normal (i e less than 5 gm per 100 cc), cyanosis cannot occur even if there is complete oxygen unsaturation i e, even if all the hemoglobin is in the reduced form

Degree of Oxygen Unsaturation

Since 1 gm of hemoglobin is capable of combining with 1 33 cc of oxygen the blood with a normal hemoglobin content (15 gm per 100 cc) has an oxygen capacity of 20 volumes per cent Actually the arterial blood (ie, after pulmonary oxygenation) contains 19+ volumes per cent of oxygen or is 95+ per cent saturated This means that there is 1 volume per cent of oxygen unsaturation of the arterial blood In passing through the tissues the blood loses an additional 5 volumes per cent of oxygen so that the venous blood has an oxygen unsaturation of 6 volumes per cent While the loss of oxygen in the capillaries is uneven, we may consider the average of the arterial and venous oxygen unsaturation $\frac{1 \text{ vol} + 6 \text{ vol}}{2}\left(= 3\frac{1}{2} \text{ volumes per cent}\right)$ as representing the average oxygen unsaturation of the capillary blood in the skin Cyanosis occurs with normal total hemoglobin content when the capillary oxygen unsaturation exceeds 6½ to 7 volumes per cent this represents 5 gm of reduced hemoglobin

This degree of oxygen unsaturation may be due to (1) inadequate pulmonary oxygenation of the blood (2) excessive loss of oxygen from the capillary blood in the tissues or (3) mixing of venous and arterial blood due to a congenital cardiovascular deformity

Cyanosis due to inadequate pulmonary oxygenation is encountered in cases of severe emphysema, kyphoscoliosis with pulmonary atelectasis pulmonary fibrosis extensive pulmonary embolization and other pulmonary disease (Chap 39)

Mild cyanosis is common in mitral stenosis in which pulmonary congestion of long duration leads to extensive fibrosis of the lung with consequent interference with oxygenation In patients with left ventricular failure there

is usually no significant arterial hypoxemia unless there is associated pulmonary edema pneumonia or other pulmonary complications which may cause cyanosis When cyanosis is present in patients with right sided heart failure it is due either to the pulmonary lesions mentioned or to the associated pulmonary congestion of left sided heart failure Oxygen therapy relieves or dispels cyanosis only to the extent that it is due to inadequate pulmonary oxygenation

Increased deoxygenation of the capillary blood contributes to cyanosis in patients with right sided heart failure It is due chiefly to slowing of the blood flow in the tissue capillaries Cyanosis may occur even with normal pulmonary oxygenation e g if 13 volumes per cent of oxygen are extracted from the capillary blood instead of the normal 5 volumes For then the average capillary oxygen unsaturation would be $\frac{1 + 14}{2} = 7\frac{1}{2}$ Often there is a combination of inadequate pulmonary oxygenation and increased capillary deoxygenation In patients with extremely diminished cardiac output especially those with acute circulatory failure cyanosis may be due chiefly to capillary deoxygenation

Cardiovascular Shunts Capillary hypoxemia sufficient to cause cyanosis may occur despite normal pulmonary oxygenation and normal capillary deoxygenation when an abnormal cardiovascular shunt causes a significant mixing of venous and arterial blood This occurs in patients with congenital cardiac malformations (p 731) such as the tetralogy of Fallot septal defects or transpositions of the great vessels Lundsgaard and Van Slyke[75] calculated that in the absence of other abnormalities cyanosis occurs if the amount of venous arterial shunt is more than about 38 per cent of the total cardiac output Less than this is necessary if as is usual there is an associated polycythemia or if pulmonary or peripheral stasis due to cardiac failure contributes to the oxygen unsaturation of the blood In many patients with congenital cardiac deformities the higher pressure in the left side of the heart as compared with the right directs the blood from the arterial to the venous side of the shunt But as a result of exercise pneumonia progressive increase in pulmonary arteriolar resistance congestive heart failure or other factors the pressure on the right side of the heart may be elevated sufficiently to produce a venous arterial shunt with the consequent development of cyanosis

THE AMOUNT OF BLOOD VISIBLE IN THE VESSELS OF THE SKIN

The intensity of cyanosis depends on the amount of reduced hemoglobin in the blood actually visible through the skin Therefore cyanosis is most readily observed where the overlying skin is very thin e g the nail beds the lips the tip of the nose the cheek bones and the ears Cyanosis is more intense the more blood and therefore the more reduced hemoglobin is actually in the vessels of the skin This in turn is greater the more numerous and the more dilated are the capillaries and venules of the skin

The state of the subpapillary venous plexus is much more important in causing cyanosis than that of the superficial capillary loops for the former presents a greater area parallel to the skin Mechanical distention of the subpapillary venules in healthy persons by compression of the arm veins can produce cyanosis even though there is a normal oxygen saturation, for although the amount of reduced hemoglobin is not elevated the amount visible is greatly increased In patients with congestive heart failure similar distention of the subpapillary venules is caused by the elevated venous pressure

FACTORS MODIFYING CYANOTIC HUE

The blue color of the skin in cyanotic patients with heart disease may vary in hue and intensity In patients with polycythemia the skin is purple or reddish blue because there is an increase in the red of the oxyhemoglobin as well as in the blue of reduced hemoglobin A pale ashen or leaden type of cyanosis is seen when the superficial cutaneous vessels are constricted and relatively empty of blood This is seen in patients with acute circulatory failure or whenever there is a sharp reduction in the cardiac output The cyanosis is then due to the reduced hemoglobin in the less visible deeper venous plexus below the skin In patients with tricuspid valvular disease and heart failure the blue of cyanosis is often mingled with the yellow color due to icterus

PATHOGENESIS OF ICTERUS IN HEART DISEASE

Jaundice is due to an excessive amount of bilirubin in the blood serum While hyper

bilirubinemia is present in many patients with congestive heart failure, it is sufficient to produce jaundice only in about 4 per cent of them, *most often in those with combined mitral and tricuspid valvular disease* [84] The significant clinical features of these cases with jaundice are severe and longstanding passive congestion of the lungs and the liver and the great frequency of pulmonary infarction[59, 100] (see p 000)

There is evidence that the hyperbilirubinemia is due to impairment of liver function This is indicated not only by the hyperbilirubinemia itself but also by the increase in urobilinogen in the urine and by various tests of hepatic function (p 00) As a rule the elevated serum bilirubin concentration is due to a mixture of quick reacting (direct) and slow-reacting (indirect) bilirubin [107] In patients *with frank jaundice associated with heart* failure there is a prompt and direct van den Bergh reaction but some patients with heart failure have a slight hyperbilirubinemia and an indirect van den Bergh reaction The impairment of liver function may be due to oxygen deficiency, and this in turn is caused chiefly by prolonged stasis of blood in the congested liver and occasionally perhaps, by deficient pulmonary aeration in consequence of extensive pulmonary infarction Both the hepatic blood flow and oxygen consumption are reduced in heart failure [88] The hepatic venous blood was found to be markedly unsaturated with oxygen [89] Clinical observations suggest that jaundice and presumably *hepatic damage in congestive heart failure are* correlated with *very* high venous pressure and prolonged duration of the latter Sherlock[111] suggested that high venous pressure may produce mechanical obstruction of the bile canaliculi with regurgitation jaundice

Hyperbilirubinemia and jaundice are caused to some extent also by excessive production of bilirubin for there is an increased quantity of urobilin in the stools as well as of urobilinogen in the urine The increase in formation of bilirubin may result from excessive destruction of blood in the lung the blood representing either infarcted areas or the red blood cells extravasated in the pulmonary alveoli Evidence of increased destruction of blood is seen clinically in the expectoration of heart failure cells and at necropsy in the deposition of hemosiderin the brown iron pigment, within the lung (brown induration) But the destruction of extravasated erythrocytes could only explain an increase in indirect bilirubin, whereas in heart failure direct bilirubin is increased to an even greater degree While pulmonary infarction may play a role in causing jaundice both by producing arterial anoxemia and by increasing the formation of bilirubin, it is not an essential factor, as jaundice in patients with heart failure may occur in its absence [8]

PATHOGENESIS OF GALLOP RHYTHM

(See p 69)

PATHOGENESIS OF PULSUS ALTERNANS
(Alternation of Pulse, Cardiac Alternans)

Pulsus alternans is an evenly spaced alternation of strong and weak cardiac or pulse beats It occurs most frequently in cases of left ventricular failure, especially those due to *hypertension or coronary atherosclerosis, but* it has been observed also in association with atrial or ventricular tachycardia Electrical alternans [84] which refers to alternation in size of the QRS or T complexes occurs in these conditions and also as a result of digitalis intoxication [87]

Pulsus alternans is distinguished from the sequence of strong and weak beats of pulsus bigeminus (p 000) by the fact that the weak beat in pulsus alternans is very slightly closer to the succeeding beat than to the preceding The weak premature beat of pulsus bigeminus is distinctly closer to the preceding normal beat

A detailed discussion of the pathogenesis of pulsus alternans may be found in the monographs of Poumailloux[93] and of Kisch [61]

The alternation in pulse is most generally attributed to a corresponding alternation in the strength of ventricular contraction and therefore in the amount of blood ejected into the peripheral arteries The interval between beats is approximately unchanged but the weak beat is slightly delayed due to slower transmission of the pulse wave In the electrocardiogram the cycle lengths are equal * The alternation in strength of cardiac contraction is believed to be due to disease or fatigue of many cardiac fibers as a result of which there is a variation in excitability or refractoriness During the strong beat most of the fibers respond but the others are refractory, during

* Friedman [36] observed that the cycle lengths are only approximately equal the cycles after the strong beats being slightly longer (I y 01–03 sec) than those after the weak beats

the weak beat fewer fibers contract including tho e which were previously refractory [12] The basic cause of pulsus alternans is severe dam age of the ventricular myocardium with im pairment of its contractility Blumberger[11] observed that the smaller systoles had a longer time of isometric contraction an anacrotic elevation of longer duration and a shorter ejection time in comparison with the larger systoles

Of interest is the observation that pulsus alternans may be initiated by a premature beat usually in cases with tachycardia in which the diastolic period is shortened The premature beat further shortens the brief diastole and significantly reduces the degree of filling and leaves many fibers refractory The subsequent compensatory pause permits greater filling and myocardial recovery Thus an alternating pattern of contraction may be initiated When associated with a tachycardia but without organic disease pulsus alternans is usually relatively benign in contrast with its serious prognostic implication in cases of left sided heart failure

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Chapter 10

CIRCULATORY AND RELATED MEASUREMENTS

THE CARDIAC OUTPUT

The cardiac output is the effective volume of blood expelled by either ventricle of the heart in a unit of time This is expressed as cubic centimeters or liters per minute The output of the two ventricles is usually identical, for the weaker musculature of the right ventricle is counterbalanced by the lesser resistance against which it works If there is a regurgitation of blood due to aortic valvular insufficiency or a shunting of blood due to congenital defects the actual output of the heart may be greater than the effective output The volume of the circulation the minute volume and the rate of circulation are used synonymously with cardiac output I prefer the latter term because of its more common usage and because the other terms may be confused with blood volume and circulation time The output of each ventricle per beat is known as the stroke output and ranges between 60 and 100 cc with an average of 75 cc when the heart rate is 72 per minute The cardiac output is equal to the stroke output multiplied by the cardiac rate Thus an increase in cardiac output may be effected by an increased stroke output an increased cardiac rate or both

MEASUREMENT OF THE CARDIAC OUTPUT

The cardiac output may be determined by

(1) Direct application of the Fick principle

(2) Dilution methods including use of foreign gases and dyes

(3) Physical methods

The Fick Principle

Fick[67] pointed out that the amount of blood traversing the pulmonary capillaries in a unit of time is a measure of the cardiac output (from the right ventricle) Since the diffusion of oxygen or carbon dioxide across the pulmonary alveolar walls depends on the pulmonary blood flow the latter can be determined from the amount of oxygen absorbed in a unit of time and the difference in oxygen concentration of the blood before and after leaving the lungs i e the arteriovenous oxygen difference It is assumed that the amount of oxidation in the lungs is negligible Thus if the oxygen concentration of the arterial blood is 190 cc per liter and that of the venous blood 150 cc per liter each liter of blood absorbs 40 cc of oxygen If 200 cc of oxygen are absorbed by the subject in one minute $\frac{200}{40}$ or 5 liters of blood must have flowed through the lungs in a minute in order to absorb this quantity of oxygen This pulmonary blood flow is the right ventricular output which is presumed to equal the left ventricular or cardiac output

Expressed mathematically

$$\text{Cardiac Output (liters per min)} = \frac{O_2 \text{ absorption (cc per min)}}{\text{Arterial } O_2 - \text{mixed venous } O_2 \text{ (cc per liter)}}$$

The cardiac output may be similarly calculated from the total carbon dioxide elimination in a unit of time and the arteriovenous carbon dioxide difference

$$\text{Cardiac Output (liters per min)} = \frac{CO_2 \text{ elimination (cc per min)}}{\text{Venous } CO_2 - \text{arterial } CO_2 \text{ (cc per liter)}}$$

The Direct Fick Method

(a) *The oxygen absorption* in cubic centimeters per minute under basal conditions is determined with the aid of a basal metabolism machine (such as the Benedict Roth apparatus) For comparative cardiac outputs e g before and after exercise the oxygen consumption can be determined from 2 or 3 minute samples of expired air collected in

Douglas bags analyzed in an Haldane apparatus and measured in a Tissot spirometer

(b) The *oxygen content of arterial blood* is found by direct puncture of a convenient artery such as the brachial, radial or femoral. An indwelling needle permits repeated sampling if multiple cardiac outputs are to be determined during a period of study.

(c) The *oxygen content of mixed venous blood* can now be satisfactorily determined from blood samples obtained by intracardiac catheterization.

For mixed venous blood satisfactory specimens in hearts without shunts are best obtained from the pulmonary artery or right ventricle. Complete mixing may not occur in the right atrium because of independent laminar flow of blood from the superior and inferior vena cava which may differ in oxygen concentration, or because of proximity to the coronary sinus, the blood from which is much lower in oxygen content than mixed venous blood. Several specimens should be taken from various parts of the chamber and they should not differ by more than 0.5 volume per cent if they represent mixed venous blood. The oxygen determinations are made as on arterial blood (p. 227).

The cardiac output is then determined by substituting the values obtained in the Fick formula

$$CO = \frac{O_2}{\text{a-v oxygen difference}}$$

There is no serious criticism of the accuracy of the direct Fick method if the technique is properly carried out by a trained team and if every effort is made to keep the patient in a physiologic state.[217, 211] However, the technical requirements make this method impractical for general clinical usage. A method has been proposed for the direct measurement of the arteriovenous oxygen difference with the aid of a photoelectric colorimeter.[116] Recently Grossman et al.[95] devised a method for determining the cardiac output by the direct Fick principle with sodium aminohippurate (PAH) or para-acetylaminohippuric acid (PACA) as the test substance, avoiding the need for gas analysis.

Dilution Methods

A measured amount of foreign gas is inhaled or a dye or other substance is injected intravenously. The amount of blood flow in unit time required to absorb the measured uptake of gas or intravenously injected material represents the cardiac output.

Foreign Gases. The methods employing *nitrous oxide* have been described in detail by Lindhard,[135] the use of *ethyl iodide* by Starr and Gamble,[195] and that of *acetylene* by Grollman.[94] These foreign gas methods are subject to error[99] and are no longer used.

Intravenous Injection of Dyes. Hamilton and his co-workers[100] have determined the cardiac output by means of the rapid intravenous injection of brilliant vital red followed by the prompt withdrawal of repeated samples of blood from the femoral artery. More recently a blue dye has been employed. One cc. of 0.5 per cent Evans blue due (T-1824) is injected rapidly intravenously and blood samples are collected immediately and continuously through an indwelling arterial needle in the femoral artery which is connected with polyethylene tubing through which the blood flows into successive tubes revolving on a kymograph.[76, 156, 117] Samples are collected for about forty seconds. The dye may also be injected at a constant rate through a catheter into the right ventricle or pulmonary artery.[180] The samples of arterial blood are analyzed for dye concentration by means of a spectrophotometer. The cumbersome multiple determinations may be obviated by the use of an automatic recording device which employs a constant flow cuvette.[158] As the blood flows through the cuvette the light transmission varies with the concentration of the dye, producing a corresponding electric current, which is amplified and continuously recorded by a sensitive recording galvanometer. Adequate precaution must be taken to maintain a constant flow of blood, otherwise changes in light transmission will be induced by change in blood flow and not exclusively by change in dye concentration. The relatively high cost and elaborate nature of the apparatus at least partially neutralize its advantages.

The determined concentrations of dye are plotted as ordinates on semi-logarithmic paper with time in seconds as the abscissa. The time of recirculation is marked clearly by a sudden change in the direction of the concentration curve thus obtained. From the concentration curve the time of one circulation and the average concentration of the dye in that circulation are determined.[11] Since the quantity of dye injected is known and the time of the first circulation and the average

dye concentration are determined by the procedure the cardiac output can be calculated as follows

$$C\,O = \frac{60 \times I}{C \times T} \times \frac{100}{100 - H}$$

in which C O is the cardiac output I is the quantity of dye injected, C is the average dye concentration in one circulation T is the duration of one circulation in seconds and H the hematocrit

Although the underlying assumptions of this method have been questioned the values obtained check satisfactorily with those determined by the direct Fick method [101 2 0 53 154] Furthermore the dye dilution method possesses the advantages that oxygen consumption is not determined cardiac catheterization is not performed, and the cardiac output can be more readily determined during exercise [1 2] The intrathoracic and pulmonary blood volumes the circulation times and the volumes of the left atrium and ventricle[33] can be determined from the curve [148 100 156] Furthermore it is possible to make multiple measurements on the same patient when it would be difficult or impossible to catheterize the heart repeatedly as would be necessary with the direct Fick procedure

On the other hand the need for multiple arterial punctures or for an indwelling arterial needle and the laborious calculations have hitherto limited the practical usefulness of the dye dilution method for determining the cardiac output A photoelectric densitometer has been devised which records dye-dilution curves of T 1824 concentrations by measuring changes in optical density of a portion of the heat flushed ear and thus obviates the need for serial samples of arterial blood [145 186] By using a multiplier phototube the device effects a linear relationship between the deflection of the recording galvanometer and changes in arterial concentration of the dye Usually only 10 mg of T 1824 are used and determinations may be repeated at short intervals There is a close correlation between cardiac outputs determined by this technique and those determined by photoelectric measurements of dye concentrations in serial arterial blood specimens The cardiac output has been somewhat similarly determined by the use of a modified Millikan ear oximeter following injection of T-1824 [225 226 84] But larger quantities of the dye are required

Intravenous Injection of Radioisotopes

A new simple technique for measuring cardiac output has recently been reported [110] The method involves a single intravenous injection of human serum albumin tagged with radioactive iodine I^{131} Following the injection the counting rate is recorded from a narrow angle scintillation counter on the skin of the first left intercostal space in the parasternal line A count rate–time curve is obtained The area under the extrapolate curve divided into the count rate at equilibrium yields cardiac output in terms of the circulating blood volume The latter must be determined by one of the available methods (infra) The accuracy of the method remains to be verified The determination of the cardiac output by a continuous recording system of radioactivity in arterial blood utilizing iodinated (I^{131}) human serum albumin, had been previously reported [172]

Physical Methods

Physical methods of determining the cardiac output have the advantage of avoiding the necessity of arterial or venous punctures or of chemical determinations However, none of the methods employed have thus far provided uniformly accurate absolute values of cardiac output In general the calculations are standardized by comparison with the direct Fick procedure Hamilton[99] has given a detailed criticism of these methods

Three physical methods have been used in humans (1) X ray measurements, (2) pulse pressure and pulse wave measurements, (3) ballistocardiography

X ray Measurement of Cardiac Output The volume of the heart is determined roentgenographically in maximum systole and diastole by synchronization of the roentgen ray machine with an electrocardiograph The surface areas are measured with a planimeter and the volumes calculated therefrom by the use of Bardeen s formula [7] The combined cardiac output of the two ventricles is equal to the difference between the calculated systolic and diastolic volumes (stroke output) multiplied by the number of cardiac contractions per minute This value must be divided by 2 to obtain the cardiac output as usually defined i e the output of either ventricle [134]

Similar roentgenologic determinations of the cardiac output have been made with the aid of the kymograph[119] or electrokymograph [174 ■] By means of the electrokymo-

gram the ventricular thickness in systole and diastole can be determined, the stroke output is then calculated by a formula using these values Twelve per cent of cardiac outputs determined in dogs by this method were found to differ by more than 25 per cent from the outputs determined by the direct Fick method [178]

Rapid serial angiocardiography (p 15) may likewise be employed to determine the cardiac output

Pulse Wave and Pulse Pressure Measurements This physical method is based on the premise that the cardiac output varies approximately as the product of the pulse pressure, the arterial distensibility and the cardiac rate [84] The distensibility of the arterial system is determined from the pulse wave velocity and the diameter of the aorta

Boger and Wezler[25] advocated the following formula for calculating the stroke output

$$S\,O = \frac{2Q \times \Delta P \times L}{g a^2}$$

in which Q is the diameter of the aorta ΔP is the pulse pressure, L is the length of the arterial compression chamber receiving blood during systole, *g* is the specific gravity of blood and a is the pulse wave velocity in cm per second Simultaneous subclavian and radial pulse tracings are made from which the pulse wave velocity and L can be determined The diameter of the aorta is estimated from roentgenograms or is taken from statistical tables based on postmortem studies

The results obtained with these methods are of dubious reliability even though they are of value in comparative determinations in the same subject Often empiric modification of the calculated outputs are necessary to bring them in alignment with determinations of the cardiac output by gasometric or direct Fick procedures Considerable experience and meticulous care are necessary in the registration of the pulse waves and in the analysis and measurement of the curves obtained The measurements of aortic diameters based on postmortem studies are considerably below actual values during life

Ballistocardiograph Cardiac outputs determined with the high frequency, undamped and with the low frequency damped ballistocardiograph have checked satisfactorily with determinations made by right heart catheterization and the Fick principle in normal subjects [42, 24, 154] The ballistocardiograph is of particular value in determining rapid changes in output in the same subject On the other hand the ballistocardiograph is not useful for the clinical study of the cardiac output in sick patients The results are unsatisfactory in cases with output regurgitation as in aortic insufficiency in patients with arrhythmias or respiratory distress, in subjects who cannot hold their breath for a few seconds, and in those with pronounced tremor The ballistocardiograph cannot be used for measurement of the cardiac output in subjects whose tracings show bizarre complexes either because of cardiac disease or some other abnormality Because the subject must lie quietly during the recording the ballistocardiograph cannot be used to determine the cardiac output during exercise

The premise underlying the use of the ballistocardiograph for determining cardiac output has been criticized [99] The calculated values are inaccurate as absolute measures of the stroke output and must be modified empirically by comparison with the direct Fick method According to Cournand, Ranges and Riley[43] a considerable error is due to underestimation of the true diameter of the aorta due to the use of tables based on measurements after death They found that the ballistocardiogram gave results which were 18 5 per cent too low By measuring the diameter of the aorta after Diodrast visualization they obtained values for the cardiac output which corresponded closely to that obtained by the direct Fick procedure

THE CARDIAC OUTPUT IN HEALTH AND DISEASE

The cardiac output under basal conditions (i e, with the body recumbent at rest, at least twelve hours postprandially and in a room at 20 C) varies between 4 and 7 liters, with an average of 5 3 liters [196] These values were obtained with the direct Fick method and cardiac catheterization but similar values have been obtained by the intravenous dye dilution method [101, 156, 117] The corresponding stroke outputs average between 70 and 80 cc

The normal value for cardiac output is more constant when expressed in terms of the surface area and averages 3 2 liters per square

meter It is somewhat higher in children The minute cardiac output per square meter is known as the *cardiac index*

The percentage of the cardiac output distributed to individual organs varies with their needs at any given moment When the requirements of an organ increase its arterioles open in response to the local accumulation of metabolic waste products or to local or axon reflexes and more of the cardiac output of blood flows to that organ With reduced activity, a reversal of these mechanisms causes arteriolar constriction and a diminution of blood flow

Determinations of the blood flow to various organs have yielded the following results

Coronary blood flow	0 25 liter per minute [95]
Renal blood flow	1 3 liters per minute[96, 98]
Cerebral blood flow	0 8 liter per minute[115]
Extremities	1 8 liters per minute
Hepatic blood flow (including viscera drained by portal vein)	1 3 to 1 5 liters per minute[97, 131]

Diminished Cardiac Output

The cardiac output is less when the subject is upright than when he is recumbent probably due to the pooling of blood in the lower extremities and consequent diminished venous return to the heart in the former position [138, 140] The cardiac output is also diminished after prolonged standing on holding the breath in inspiration and in persons of advanced age Anxiety may be associated with an elevation in cardiac output [106]

Pathologic Conditions Associated with a Diminished Cardiac Output

1 Myxedema (p 1017)

2 Constrictive pericarditis (p 610) and occasionally pericarditis with effusion (p 594)

3 Paroxysmal tachycardia and atrial fibrillation with rapid ventricular rate—due to the diminished period of diastole and consequent reduction in diastolic filling (Chapter 14)

4 Heart block occasionally when the increased stroke output is insufficient to compensate for the slow cardiac rate (p 390)

5 Shock states (Chapter 12)

6 Valvular heart disease particularly aortic stenosis or mitral stenosis is often associated with a diminished cardiac output The cardiac output may be normal when the patient is at rest but increases less than normally with exercise The cardiac output may fail to increase with exercise

7 Congestive heart failure (This is discussed in detail in Chapter 8) Usually there is a decrease but the cardiac output may be normal With exercise there is little or no increase in cardiac output in contrast with the pronounced augmentation in normal individuals [104]

8 Atrial fibrillation Most observers have found the cardiac output diminished by 20 to 30 per cent with a corresponding increase when regular rhythm is reestablished by quinidine (p 359)

Increased Cardiac Output

The cardiac output is *increased* most commonly as a result of muscular exercise Digestion may increase the cardiac output by 30 to 40 per cent one hour after a meal and the increase may persist for three hours Emotional excitement may produce a similar increase The increase in cardiac output and consequent increase in the work of the heart may account for the precipitation of attacks of angina pectoris in susceptible patients following exercise meals or excitement The cardiac output is increased after the ingestion of fluids and after intravenous infusions in therapeutic doses Pregnancy is associated with an elevation of cardiac output varying between 30 and 50 per cent (p 1087) A rise in environmental temperature to above 30 C and the initial period of exposure to high altitudes are associated with increased cardiac output

Pathologic Conditions Associated with Increased Cardiac Output

1 Hyperthyroidism (p 1001)

2 Fever The increase as in Graves disease is due to the elevated metabolism The systolic output is unaltered or slightly diminished so that the increased cardiac output corresponds to the rise in heart rate

3 Anemia (p 1048)

4 Arteriovenous fistula (p 694)

5 Beriberi (p 1039)

6 Severe pulmonary emphysema (p 989)

7 Osteitis deformans

THE CIRCULATION TIME

The determination of the speed of blood flow is of clinical value because of its distinctive alteration in congestive heart failure and other circulatory disturbances Clinical

methods do not actually measure the velocity of the blood flow, which varies considerably in diverse parts of the vascular tree owing to differences in the caliber of arteries, capillaries and veins. The *circulation time* measures the shortest interval between the injection of a substance into a vein and its arrival at some distant site in sufficient concentration to produce a recognizable end point. It represents approximately the inverse of the average velocity of blood flow between two points.

The circulation time is related to both the cardiac output and the volume of the circulating blood. The circulation time tends to increase as the blood volume increases. The circulation time tends to diminish as the cardiac output increases, for the latter indicates that there is a greater volume of blood passing a given point in a given time. Unless the caliber of the vessel is enlarged, this is possible only if the speed of the circulation is increased. However, the circulation time may remain unchanged if there are simultaneous and similar increases in cardiac output and blood volume. This relationship may be expressed mathematically

$$CT = k\frac{BV}{CO}$$

in which CT represents the circulation time, BV the circulating blood volume, CO the cardiac output per minute and k a "constant" which however is undetermined and which in fact may vary somewhat in different individuals or even in the same individual under changing conditions. It is apparent from the above formula that the circulation time is most likely to be prolonged if there is both an increase in the blood volume and a diminution in cardiac output, findings typical of advanced congestive heart failure.

METHODS OF DETERMINING THE CIRCULATION TIME

The usual technique is to inject rapidly a foreign substance into a peripheral vein and to note the time elapsing between the injection and the arrival of the substance at some other point in the circulation. Koch[10] first employed fluorescein, but his method was impractical because of the need for multiple venipunctures. Fundamental work on the circulation time was contributed by Blumgart and Weiss.[4] They injected radium C into an antecubital vein and detected its arrival in the right side of the heart (arm-to-right heart time) and in the opposite antecubital artery (arm-to-arm time) by a special radiosensitive device.

Clinical Methods

The clinical methods which are used most generally measure the arm-to-tongue time and employ solutions of either Decholin, saccharin or calcium gluconate as the injected material. Volatile substances such as ether are often injected intravenously in order to determine the arm-to-lung time. These substances have the disadvantage of producing subjective end points. Consequently, the patient's reaction time and degree of cooperation are factors which may affect the result.

The test is performed with the patient recumbent after having rested at least twenty minutes. He should be reassured so that he is relaxed and his pulse and respiration are basal. In particular, he must be told not to hold his breath after insertion of the needle, as this may retard the venous return to the heart. The nature of the end point, such as a sweet or bitter taste, should be explained to the patient as well as the importance of his announcing it *immediately* by some agreed signal such as "now" or "sweet." After the tourniquet is applied and the needle inserted, the tourniquet should be released and 20 to 30 seconds allowed to elapse to permit reestablishment of the normal circulation in the vein before the injection is made. It is essential that the quantity of solution used be small enough and the bore of the needle large enough (about 18 gauge) to permit *rapid injection* (less than a second). A stop-watch is started at the instant the injection is begun and stopped when the patient signals the end point or when an objective end point is noted. Whenever possible the test should be repeated after a few minutes to check the result. Some of the substances most commonly used for the determination of the circulation time, their doses and end points are the following:

Decholin (sodium dehydrocholate)
- Quantity: Five cc. of a 20 per cent solution
- End point: Bitter taste and involuntary grimace
- Normal arm-to-tongue time: 10 to 16 seconds.[203]
- Comment: Sharp and usually reliable end point but relatively expensive. Occasional reaction.[182]

Saccharin (sodium benzosulfimide)
- Quantity: 2.5 cc. prepared by dissolving 2.5 gm. of soluble saccharin (Merck) in 2 cc. distilled water and heating *just enough* for solution

End point Sweet taste
Normal arm-to-tongue time 9 to 16 seconds[74]
Comment Cheap Small volume of solution needed Local venous thrombosis and painful swelling if perivenous tissue is infiltrated

Calcium gluconate
Quantity 3 to 5 cc of a 20 per solution
End point Hot sensation in tongue and pharynx
Normal arm-to-tongue time 10 to [illegible] seconds[84]

Magnesium sulfate
✓Quantity 10 cc of a 10 per cent solution (Also a mixture of magnesium sulfate and calcium gluconate has been used[194])
End point Hot sensation in tongue and pharynx
Normal arm-to-tongue time [illegible] to 17 seconds[17]

Fluorescein or Riboflavin
Quantity 2 cc of a 20 per cent or 3 cc of a 15 per cent solution of sodium fluorescein *or* 0 8 mg per kilo body weight of riboflavin[223]
End point Greenish yellow fluorescence in mucous membrane of lips or tongue[184] or in previously prepared histamine wheal of arm[312] Visualized in dark with source of ultraviolet light
Normal arm-to-lip time 10 to 16 seconds
Comment Objective end points

Alpha Lobeline
Quantity 0 5 cc of a 1 per cent solution
End point Cough usually with a grimace and hyperpnea[14]
Normal mean 11 to 12 seconds
Comment Unpleasant side actions

Sodium succinate
Quantity 1 5 cc of a 30 per cent aqueous solution of disodium succinate hexahydrate
End point Elevation of cricoid choking sensation cough
Normal arm-to-throat time 12 to 10 seconds (mean 15 8 sec)[8]

Radioactive Sodium
The circulation time may be determined by injecting radioactive sodium (Na^{24}) intravenously and clocking its arrival at any distant point by a Geiger Mueller counter[103]

Ether
✓ Quantity 5 minims ether and 10 minims normal saline[106] (1 4 cc paraldehyde may be substituted)[14]
End point Facial grimace cough ether taste or smell
Normal arm-to-lung time 4 to 8 seconds

Carbon Dioxide
Quantity Inhale 30 per cent mixture carbon dioxide in air[8]
End point Acceleration and deepening of respiration
Lung-to-carotid sinus time [illegible] to 10 seconds

Nitrogen or Helium
While the oximeter is measuring the arterial oxygen saturation in the ear the subject inhales a single breath of 100 per cent nitrogen or helium[69] The end point is a reduction in arterial oxygen saturation at the site of the oximeter This measures the lung-to-ear time[271]

Evans Blue (T 1824)
This has been used in diagnosis in congenital heart disease (p 759)

CLINICAL ABNORMALITIES OF THE CIRCULATION TIME

Diminished Circulation Time

The circulation time is *reduced* in the following pathologic conditions

1 Hyperthyroidism (p 1002)
2 Anemia (p 1017) The reduction in circulation time with both primary and secondary anemias parallels the severity of the anemia[203, 84]
3 Beriberi heart disease (p 1039)
4 Arteriovenous fistula (p 694)
5 Pregnancy (p 1088)
6 Congenital heart disease (p 797)
7 Febrile states Acceleration of the circulation is the result of peripheral vasodilatation

The circulation time is also reduced during digestion and after exercise Because of these effects *the circulation time should be determined when the patient is in a basal state*

Prolonged Circulation Time

A *prolongation* of the circulation time is observed in the following pathologic conditions

1 Congestive heart failure (p 107)
2 Polycythemia vera The slowing of the circulation[3] is dependent on the increase in circulating blood (erythrocyte) volume and the associated increase in viscosity of the blood
3 Myxedema (p 1018)

The circulation time is normal in cases of compensated valvular heart disease or hypertension *If the circulation time is prolonged in* these conditions careful investigation usually elicits some subjective or objective evidence of cardiac failure

DIAGNOSTIC VALUE OF THE CIRCULATION TIME

The chief use for the determination of the circulation time is in confirming the diagnosis of congestive heart failure By performing both an arm-to-tongue and arm-to-lung test and determining the venous pressure at the same time the cardiac failure may be attributed to the left or right side of the heart or both Prolongation of the arm-to-tongue (saccharin Decholin) time with a normal arm-to-lung (ether) time and a normal venous pressure usually denotes pure left-sided failure prolongation of both and elevation of the venous pressure indicate right-sided heart failure The simplicity of these tests which can

be readily performed both in the office and at the bedside makes them an integral part of the examination of the circulation

Often the circulation time helps to distinguish cardiac failure from a number of conditions which produce some of the same symptoms

1 **Asthma** In cases of bronchial asthma the circulation time is normal or it may be reduced Asthma due to heart failure is associated with a prolonged circulation time A normal circulation time usually excludes cardiac *failure* but not cardiac *disease*

2 **Dyspnea and Orthopnea** When dyspnea or orthopnea is due to intrinsic pulmonary disease without heart failure the circulation time is normal[16] But in cases of severe emphysema with diminished arterial oxygen saturation the circulation time may be diminished In cases of complete unilateral pneumothorax it may be rapid Dyspnea or orthopnea due to congestive heart failure is accompanied by a long circulation time

3 **Edema or Ascites** Edema due to nephritis nephrosis, postural defects or local venous disturbance and ascites due to cirrhosis of the liver or neoplasm, are associated with a normal circulation time In cases of anemia with edema there may be a normal or an abbreviated circulation time

4 **Hepatic Enlargement and Venous Engorgement** A determination of the circulation time may aid both in distinguishing hepatic enlargement due to heart failure from that due to intrinsic disease of the liver and in distinguishing the cervical venous engorgement of heart failure from that due to superior vena caval obstruction

The circulation time has been found of value in revealing obscure cases of hyperthyroidism This may be suspected when the circulation time is normal in an obvious case of congestive heart failure without associated severe anemia or avitaminosis The use of the circulation time measurements in the diagnosis of congenital heart disease is discussed on page 797

The circulation time is helpful in estimating the progress and prognosis of a patient with congestive heart failure As signs and symptoms of congestive heart failure regress the circulation time diminishes and may revert to normal It has been noted however, that the circulation time may increase although distressing dyspnea or orthopnea subsides when right sided heart failure is added to pure left-sided failure As a rule, a reduction in the long circulation time indicates improvement

VENOUS PRESSURE

Clinical measurement of the venous pressure is limited to the systemic (caval) venous branches However, an elevation of the pulmonic venous pressure can often be surmised when there are physical signs of congestion or edema of the lungs or roentgenologic evidences of pulmonary congestion in patients with cardiac disease

It is clinically desirable to determine the pressure in the systemic veins near their entrance into the right atrium As a rule the pressure in these great veins is not determined directly instead some more accessible vein nearby such as the external jugular vein or an antecubital vein is used To eliminate the factor of hydrostatic pressure the patient is examined in the supine position with the vein under consideration placed at the level of the right atrium This may not be a precise correction for there is some evidence that the zero reference point is not at the level of the base of the atria but some distance below[36] The mean right atrial pressure in normal subjects is -2 to $+2$ mm Hg relative to atmospheric pressure[22]

The measurement of the venous pressure can be made by clinical inspection, by indirect methods or by direct cannulation of a vein

Estimation of the Venous Pressure by Clinical Inspection

It was suggested by Gaertner[78] that when an extremity is elevated its veins represent a manometric column in communication with the right atrium The arm is elevated until a visible vein collapses At this point the venous pressure is just balanced by the hydrostatic pressure in the vein The height of the collapsed vein above the level of the atrium represents the venous pressure This method is useful only when the venous pressure is higher than normal The veins on the under-surface of the tongue have also been used to determine an elevation in venous pressure[11] Normally these are collapsed when the patient is sitting They become notably engorged when the venous pressure exceeds 20 cm of water

The use of the external jugular vein for estimating venous pressure has been emphasized by Lewis[123] Normally when the subject

sits or stands erect this vein fills to the root of the neck the height of filling increasing as the subject becomes more horizontal When the subject is recumbent the venous filling reaches a point which is on a horizontal level with the lower border of the manubrium sterni or the zero point of reference If the venous pressure is increased above normal the level of venous filling is correspondingly elevated Thus with congestive heart failure the jugular vein may be visibly filled for 2 or more cm above the level of the clavicle even when the patient is upright As the head and shoulders are lowered the height of venous filling increases and may reach to the angle of the jaw If the height of filling is not distinct gentle pressure over the lower end of the vein for a few minutes will accentuate the filling the pressure is then released and the vein observed again

Sometimes it is simpler to observe the jugular venous pulse The highest point to which this rises gives the level of venous filling and consequently measures the venous pressure When the superficial veins of an extremity are clearly visible e g, on the dorsum of the hand the venous pressure may be roughly estimated as the height to which the extremity must be elevated above the atrium in order to cause the vein to collapse

Indirect Method of Determining Venous Pressure

The indirect method[9] involves the determination of the external pressure necessary to cause a superficial vein to collapse this pressure being equal to the venous pressure A transparent, sometimes illuminated capsule with grooved edges is sealed with collodion over the vein to be studied Air is introduced into the capsule by an air pump or bulb until the vein collapses, while at the same time a connecting water manometer is observed for the exact pressure at which venous collapse is effected The system must be airtight The venous pressure can be determined in any position of the patient and the hydrostatic pressure may then be eliminated by subtracting the vertical height from the vein to the level of the manubrium sterni This method is too inaccurate for general clinical use

Direct Methods of Measuring Venous Pressure

Stephen Hales[98] first made direct measurements of the venous blood pressure by noting the height to which the blood rose in tubes inserted into the jugular vein of animals Present direct methods include that of Moritz and Tabora[149] or some modification such as that of Taylor Thomas and Schleiter[204] My experience is concerned chiefly with the latter method which I have found eminently satisfactory for practical bedside use The modification proposed by Griffith et al[93] or by Sodeman[193] has also been extensively used An aneroid type of manometer (phlebomanometer) was devised by Burch and Winsor[31]

Method of Moritz and Tabora[149] Insert into the median basilic vein a needle connected by adapter and tubing to a calibrated buret containing saline The saline and the apparatus must be sterile The saline is allowed to enter the vein until the inflow ceases At this point the level of the saline above that of the right atrium represents the venous pressure Moritz and Tabora[149] found the normal venous pressure to vary between 1 and 8 cm water and most frequently between 4 and 8 cm

Method of Taylor Thomas and Schleiter[204] A sterile L shaped calibrated glass tube 30 cm in length and of 4 mm bore is used the short limb being ground to fit an 18 gauge intravenous needle The tube or manometer is moistened with 5 per cent sodium citrate solution to inhibit coagulation The patient is supine with his upper extremity relaxed and abducted from the body at an angle of about 60 degrees This is to avoid compression or torsion of the axillary or subclavian vein when the arm is close to the body (If the patient is very orthopneic, the venous pressure may be determined with the patient seated, but the reference level for the zero mark should be the horizontal plane 4 cm below the fourth sternocostal junction [illegible]) The subject should rest at least 15 minutes before the procedure is begun A pillow or towel are placed under the arm to be used so that the antecubital vein is 5 cm below the horizontal plane of the anterior surface of the sternum at its fourth costochondral junction This represents approximately the level of the opening of the venae cavae into the right atrium The patient is instructed to relax and breathe naturally to avoid muscle [illegible] abnormal changes in intrathoracic pressure

A sphygmomanometer cuff applied [illegible] arm is inflated to 40 mm Hg or a tourniquet may be used The needle is inserted [illegible] into a large antecubital vein so as to [illegible] free flow of blood and the [illegible] pressure [illegible]

flated In the lower extremity the femoral vein may be used, the puncture being made upward and inward 2 5 cm distal to the inguinal ligament and just medial to the pulsating femoral artery The height of the column of blood, when it comes to rest in the tube, *represents the venous pressure* Consecutive readings should be made until they are constant The presence of a free communication with the blood stream is indicated by small excursions of the blood in the tube during respiration by a rise of the blood level in the tube when the cuff is inflated again and by a return to the previous level when deflated

It is apparent that because of gravity, the venous pressure is considerably higher especially in the lower extremity when the subject is standing than when he is recumbent To neutralize this hydrostatic effect the vein used for measuring pressure is kept at that level in the right atrium at which the pressure is zero This is known as the zero or reference level I have generally used a level of 5 cm below the horizontal level of a plane through the fourth costochondral junction, depending on the approximate thickness of the chest wall Lyons et al [138] have used a level 10 cm above the level of the skin of the subject's back when in the recumbent position and Hussey [113] the midaxillary line Winsor and Burch[224] have used a "phlebostatic level" which for the supine position is a horizontal plane half the distance from the base of the xiphoid to the table and *in the upright position* through the fourth intercostal space These *reference levels are equally valuable if consistency is maintained in all readings*

Aneroid Phlebomanometer of Burch and Winsor[31] This is an aneroid type of manometer calibrated in millimeters of water The pressure in the vein is balanced by the pressure in the manometric system which is attained by *mechanical compression of a* pressure bulb A glass adapter of 1 mm bore containing citrate solution connects the manometer to a 23 gauge needle which is inserted into an appropriate vein When the column of citrate solution balancing the venous blood pressure comes to rest the pressure is read from the scale of the manometer *The aneroid* manometer should be checked from time to *time* against a direct water manometer

Normal and Pathologic Venous Pressures

The normal venous pressure in an antecubital vein at the level of the right atrium is 4 to 8 cm water as determined by the direct method Greater variations have been noted by Moritz and Tabora[149] (1 to [illegible] cm), by Hussey [11] (4 to 12 cm) by Lyons et al [138] and Winsor and Burch[224] (5 to 14 cm) In my experience with the method of Taylor and his co workers [204] *the normal venous pressure* rarely exceeds 10 cm or falls as low as [illegible] cm water The venous pressure is the same in the upper and lower extremities when the veins are at the reference level of the heart [93, 224] The venous pressure in children is essentially identical with that in adults [126]

The venous pressure is increased by exercise, but usually returns to normal or lower *within a minute after its cessation* [201] With heart failure, the elevation is much greater and *it returns slowly to its previous level* [3] The venous pressure falls about 0 5 cm with quiet inspiration and rises to the same degree with normal expiration Cough and the Valsalva test increase the venous pressure The Muller experiment diminishes the venous pressure An infusion of 500 to 1500 cc of normal saline or of 5 per cent glucose solution may cause a significant increase in venous pressure only if more than 20 cc per minute is administered [49]

The venous pressure is elevated in the following *pathologic conditions*

1 *Right sided heart failure* Usually the venous pressure is between 10 and 20 cm , but it may rise as high as 30 cm or more Occasionally the venous pressure is only slightly elevated or even normal despite the presence of distinct hepatic enlargement and subcutaneous edema In such cases compresssion of the abdomen causes an elevation of venous pressure of 2 cm of water or more [178, 106] At the same time the jugular veins may become visibly engorged The more advanced the heart failure the higher the venous pressure *and the greater the elevation following* abdominal compression In normal subjects abdominal pressure causes no change or more often a slight fall in venous pressure in the upper extremity (p 154) [107] In some patients with mild or potential right heart failure the venous pressure may be normal at rest but abnormally elevated during exercise such as repeated flexion or elevation of the legs [201, 83, 3]

In pure left sided failure the systemic venous pressure is normal The venous pressure is often below 10 cm in patients with cardiac dyspnea and orthopnea and a prolonged

circulation time Presumably the pulmonary venous pressure is elevated (cardiac catheterization) Indirect evidence of elevated pulmonary venous pressure and venous engorgement are the prolonged circulation time and pronounced reduction in vital capacity In peripheral circulatory failure and in cardiac shock with strikingly diminished output the venous pressure is reduced to 3 cm or less In cases of acute coronary occlusion there is often a combination of shock and congestive heart failure the venous pressure depending on which factor predominates Sometimes in cases of shock the veins of the extremities are collapsed but the jugular veins are engorged and their pressure high

2 Constrictive pericarditis The venous pressure is extremely high usually above 20 cm Even slight abdominal compression causes a sharp rise so that the pressure exceeds 30 cm and the blood flows over the top of the tube

3 Pericardial effusions with cardiac tamponade

4 Thrombosis of the venae cavae

5 Mediastinal tumors aortic aneurysm etc [112]

6 Obstructive emphysema and bronchial asthma when associated with an increased intrapleural pressure and consequently with increased resistance to venous inflow [1, 2] The majority of patients with pulmonary emphysema have a normal venous pressure but in many cases an elevated venous pressure reflects increased intrapleural pressure

7 Local venous obstruction due to compression or thrombosis

Clinical Application of Determination of Venous Pressure

The chief value of determining the venous pressure is in the diagnosis and differential diagnosis of right sided congestive heart failure This diagnosis is usually indicated especially in a patient with known cardiac disease if the venous pressure is elevated or if it rises more than 1 cm after abdominal compression Other causes of elevated antecubital venous pressure can usually be excluded by roentgenologic examination of the chest with special reference to the lungs aorta and mediastinum Simultaneous determinations of the venous pressure and circulation time distinguish pure left-sided heart failure pure right sided heart failure and combined heart failure [114]

In right-sided heart failure the venous pressure is universally elevated Universal elevation of the venous pressure i e in the upper and lower halves of the body is also observed in cases of constrictive pericarditis and pericardial effusion with tamponade Obstruction to the superior vena cava by aortic aneurysm mediastinal or pulmonary masses or thrombosis produces an increased venous pressure only in the upper extremities Clinical inspection will also show venous engorgement limited to the upper part of the body Furthermore there is usually a visible collateral circulation in the anterior chest wall with a flow of blood from above downward Neither right-sided heart failure nor constrictive pericarditis produces sufficient venous obstruction to lead to the development of a visible collateral circulation I have seen a case of thrombosis of the superior and inferior venae cavae of unexplained etiology which caused a universal elevation of venous pressure but this generalized elevation of venous pressure could be distinguished from that due to heart failure because there was a visible collateral circulation in the chest wall

Obstruction to the venous return through the inferior vena cava produces an elevated venous pressure only in the lower extremities This may be observed with pregnancy abdominal tumors with and without ascites hypernephroma and other renal tumors invading the inferior vena cava hepatic tumors and thrombosis of the inferior vena cava [113]

A local venous obstruction e g in a subclavian vein will cause an elevation of venous pressure only in peripheral veins of the affected arm Obstruction due to an aneurysm of the aorta usually causes greater elevation in the left than in the right arm

In cases of constrictive pericarditis the venous pressure is extremely high and the elevation after abdominal compression is usually greater than in cases of right-sided heart failure secondary to left sided failure Furthermore the circulation time may be normal in contrast with the prolonged circulation time in the latter cases In cases of cardiac tamponade the high venous pressure is associated with a small pulse a low blood pressure and the clinical picture of shock

Comparative measurements of the venous pressure in the upper and lower extremities are of diagnostic value in distinguishing heart failure from superior vena caval obstruction

They also differentiate hepatic enlargement, edema and ascites due to right heart failure from similar findings due to other conditions [66] When enlargement of the liver is due to neoplasm or cirrhosis or when peripheral edema is due to nephritis avitaminosis, or local orthopedic or venous abnormalities in the legs without associated right sided heart failure the venous pressure in the arm veins is normal *The venous pressure in the lower extremities* may or may not be elevated

Repeated determinations of the venous pressure are valuable in the prognosis and treatment of right sided heart failure Improvement is frequently denoted by a progressive diminution of the venous pressure Conversely, a persistently high venous pressure despite rest in bed sodium restriction and the administration of digitalis and mercurial diuretics indicates a poor prognosis In cases of constrictive pericarditis these measures do not significantly reduce the venous pressure but effective surgical release of the heart is followed by a return of the venous pressure to normal

BLOOD VOLUME

The blood volume refers to the volume of the circulating blood Direct measurements *of the blood volume have been made by* exsanguinating animals or decapitated criminals By this means, the blood volume in humans was found to be one thirteenth of the body weight or between 5 and 6 liters For clinical purposes indirect methods must be utilized to determine the circulating blood volume [m] A known quantity of a foreign substance is introduced into the blood and its concentration in a sample of blood is determined some minutes later, when thorough mixing has occurred From these two values the blood volume can be calculated by dividing the quantity of injected material by its concentration in the blood at the time of uniform mixing The foreign substance must be non toxic in the quantity used must become evenly distributed in the blood, and must not diffuse out of the blood to any significant degree within the period of the test and its concentration in the blood must be readily determinable

One group of substances such as the dye Evans blue (T-1824) or radioiodinated plasma albumin are distributed throughout the plasma and are used to determine plasma volume Others, such as carbon monoxide radioactive P^{32} or radioactive chromium Cr^{51} are attached to and label only the erythrocytes and are used to determine red cell volume The blood volume is calculated from the determined plasma volume and hematocrit

$$\text{Blood Volume} = \frac{\text{Plasma Volume}}{100 - \text{Hematocrit}} \times 100$$

or the blood volume is calculated from the de termined red blood cell volume and the hematocrit

$$\text{Blood Volume} = \frac{\text{Red Blood Cell Vol}}{\text{Hematocrit}} \times 100$$

The blood volume may also be calculated by determining the plasma volume and the red cell volume individually and simultaneously with different test substances, and adding the two values

Determinations of total blood volume calculated from the hematocrit i e the relative erythrocyte volume $\left(\frac{\text{red cell volume} \times 100}{\text{total blood volume}}\right)$ measured by centrifuging blood from a large vein such as the antecubital, differ significantly from the more accurate total blood volume calculated from simultaneously determined plasma volume and red cell volume This is due to the fact that capillaries and small vessels contain less red cells and more plasma than large veins hence the over all cell volume per cent throughout the circulation is less than the venous cell volume per cent (venous hematocrit) [m, 87, 8, 87, 108] Trapping of plasma among the erythrocytes also tends to increase the measured venous hematocrit The ratio of the

$$\frac{\text{over all cell per cent (body hematocrit)}}{\text{venous cell per cent (venous hematocrit)}}$$

is fairly constant, namely 0 91 [35] Therefore the total blood volume tends to be underestimated when it is calculated from the red cell volume and venous hematocrit This must be considered in interpreting some of the recent reports of blood volume in congestive heart failure (p 166) If the $\frac{\text{total body hematocrit}}{\text{venous hematocrit}}$ is even lower than normal in congestive heart failure, as recently *reported* [108, 109] *the blood volume in* congestive failure would be especially underestimated in this condition when calculated from the red cell volume and venous hematocrit

DETERMINATION OF THE CIRCULATING BLOOD VOLUME

Evans Blue (T 1824)

This blue dye has been found preferable to the red colloidal dyes because its estimation is not impeded by similarity to the inherent color of plasma or by the occurrence of hemolysis The details of the method using Evans blue are reported by Gibson and Evans [illegible] and modifications have been described by others [80, 4, 170, 87, 49, 189]

Method The subject s height and weight are taken and his surface area calculated The determination should be made under basal conditions with the patient in the fasting state recumbent and resting at least twenty minutes

About 10 cc of blood is withdrawn without stasis into a dry centrifuge tube containing oxalate or heparin and the tube is inverted several times

Exactly 5 cc of a 0 5 per cent solution of Evans blue (T 1824) is injected intravenously

In 10 minutes exactly 10 cc of blood is withdrawn from another vein without stasis and added to a dry tube containing anticoagulant In cases of heart failure or shock this sample of blood is removed after 15 minutes because of the longer time required for uniform mixing of the dye

From the first tube enough blood is put into a Wintrobe tube and the hematocrit determined by centrifuging for 1 hour at 3000 R P M

The remainder of the dye free specimen as well as the specimen of blood containing dye is centrifuged

The dye free plasma is drawn off and read as a blank in the colorimeter and the plasma containing dye is likewise read in the colorimeter

From the prepared curve the plasma volume is calculated and the red cell volume and total volume determined from the hematocrit

For greater accuracy multiple specimens of blood should be taken at intervals of five ten fifteen and twenty minutes after injection of the dye and appropriate calculations made from the mixing curve obtained from the concentration values of the dye in these specimens A modification of the dye dilution method for serial estimation of plasma volume recently described by Plentl and Gelfand [169] is said to provide increased accuracy in administration of the dye and thus permit a reduction in the amount of dye used for each determination (3 to 4 mg instead of 15 to 20 mg)

The dye method has been criticized for yielding purportedly high values for plasma and blood volumes due to rapid passage of dye out of the blood stream into the lymphatics [illegible] However there is substantial evidence that this loss of dye is not significant during the test period and that T 1824 yields essentially reliable values for plasma volume [187, 188]

Radioactive Substances

The plasma volume may also be determined by the intravenous injection of serum albumin or plasma of which the albumin has been tagged with radioactive iodine I^{131}, [illegible, illegible, 13, 107] or with radioactive chromic chloride Cr^{51} [77]

The erythrocyte volume formerly determined by having the subject inhale carbon monoxide[44] or by injecting a donor s erythrocytes tagged with radioactive iron Fe^{59} by previously feeding the Fe^{59} to the donor [51] has more recently been measured by injecting erythrocytes more simply tagged in vitro with radioactive phosphorus P^{32} [164] radioactive chromium Cr^{51} as sodium chromate [88] or radioactive thorium B [103, 16] Various advantages have been noted for the use of radiochromium[88, 103, 174] and of thorium B[103] over previous methods employing radioiron or radiophosphorus

To avoid errors due to calculating the blood volume from the venous hematocrit the total blood volume has been measured by separate individual determination of the plasma volume and the erythrocyte volume This has been accomplished by simultaneous determination of the plasma volume with T 1824 or radioiodinated plasma albumin and of the erythrocytes by radiophosphorus[15] or radiochromium Plasma and erythrocyte volumes have also been determined simultaneously by using Cr^{51} as chromic chloride to determine plasma volume and as sodium chromate to determine red cell volume [87]

THE NORMAL CIRCULATING BLOOD VOLUME

The normal circulating plasma is approximately 4 to 4 5 per cent of body weight or 40 to 45 cc per kilogram This corresponds to a total blood volume of 70 to 80 cc /kg [80] The blood volume is about 10 per cent higher in

males than in *females*, chiefly owing to a greater red cell volume in males In obese persons the circulating blood volume is lower in relation to body weight than the average values stated, while in lean or emaciated persons it is higher The normal blood volume has a more constant value when related to surface area than to body weight But in persons who have undergone considerable changes in weight due to disease obesity or accumulation of edema the most accurate standards of blood volume are obtained when related to height

The reported values for plasma erythrocyte and total blood volumes vary according to the method employed The values for plasma volume determined by radioactive iodinated serum albumin and by T 1824 do not differ significantly [48, 137] But total blood volumes based on measured plasma volume and the hematocrit tend to be 10 to 20 per cent higher than those calculated from the measured red cell volume and hematocrit,[1] or from simultaneous individual determination of plasma volume and erythrocyte volume Thus Nachman et al [152] found an average plasma volume of 44 cc /kg with T 1824, an average erythrocyte volume of 29 cc /kg with radioactive phosphorus P^{32} and a total blood volume of 73 cc /kg But the total blood volume calculated from the T-1824 plasma volume and average venous hematocrit of 44 8 was 81 cc /kg and that calculated from the P^{32} erythrocyte volume and hematocrit was 65 cc /kg Simultaneous determinations of plasma volume by chromic chloride Cr^{51} and of erythrocyte volume by sodium chromate Cr^{51},[87] yielded values of 41 cc /kg for plasma 30 cc /kg for erythrocytes, and 71 cc /kg for total blood volume—values only slightly different from the values quoted above from Nachman et al [152] In terms of surface area the mean plasma volume is 1 5 liters per square meter the red cell volume 1 1 liters per square meter and the total blood volume 2 6 liters per square meter The blood volume in infants and children is much higher relative to body weight and surface area [181, 156]

The various methods of tagging erythrocytes with radioactive materials Fe^{59} P^{32} or Cr^{51} yield similar values The P^{32} technique has disclosed a mean erythrocyte volume of 30 cc /kg for males and 27 cc /kg for females [15] the radiochromium technique yielded a mean erythrocyte volume of 30 cc /kg [87] and thorium B, 30 to 35 cc /kg [182] Nomof and associates[159] noted that the erythrocyte volume as determined by carbon monoxide (34 cc /kg), was 16 per cent higher than by radiochromium (28 2 cc /kg)

In attempting to overcome the error due to calculating the total blood volume from erythrocyte volume and hematocrit the radioactivity after equilibrium has been measured in whole blood instead of in the centrifuged tagged red cells [190, 174, 16, 168] However, although the injected radioactive material may become uniformly distributed among the erythrocytes of the circulation, it is not uniformly distributed in the blood throughout the circulation since the relative red cell volume is less in capillaries and small vessels than in the large vessels from which blood is drawn for analysis[103] (p 220)

PHYSIOLOGIC AND PATHOLOGIC VARIATIONS IN BLOOD VOLUME

Increased Blood Volume

The circulating blood volume is *increased* with elevation of the environmental temperature with altitude during muscular exercise intense emotion and progressively during the latter half of pregnancy (p 1088) The blood volume increases temporarily following rapid transfusions and infusions or after the oral administration of large amounts of sodium salts [137]

The following *pathologic conditions* are also associated with an increase in blood volume which may be due essentially to an increased plasma volume, an increased cell volume or both

1 Polycythemia vera and secondary polycythemia (chiefly or exclusively red cell volume)

2 Leukemia (white blood cells and plasma)

3 Cirrhosis of the liver (plasma)

4 Splenomegalic anemias (plasma increased red cells diminished)

5 Hyperthyroidism (red cells and plasma—slight)

6 Cushing s syndrome (chiefly erythrocytes)

7 Congestive heart failure (p 166)

Diminished Blood Volume

The circulating blood volume is *reduced* on exposure to cold after sweating after prolonged abstinence from fluids, after anes

thesia and after standing erect for one-half hour or more It is also reduced by a low salt diet and by diuretic drugs such as the mercurials, acidifying salts or urea

The most important *pathologic conditions* associated with a reduction in the circulating blood volume are

1 Hemorrhage (plasma and cells)

2 Various forms of shock (see Chapter 12)

3 Diseases associated with severe diarrhea (plasma)

4 Diseases associated with persistent vomiting (plasma)

5 Myxedema (red cells and plasma—slight)

6 Chronic glomerulonephritis (red cells reduced plasma increased)

7 Severe pernicious anemia (red cells greatly reduced plasma increased slightly)

THE INTRATHORACIC BLOOD VOLUME

The intrathoracic blood volume has been regarded as an important factor in determining clinical manifestations in congestive heart failure particularly in cardiac disease associated with left sided heart failure The intrathoracic blood volume has been determined by the T 1824 dye method used to measure the cardiac output (p 210) The dye is injected intravenously or through a catheter in the pulmonary artery The blood between injection and sampling points termed the intrathoracic blood volume the central or the pulmonary blood volume may be calculated by multiplying the blood flow and the mean circulation time as determined from the dye concentration time curve [199, 148, illegible, 150, 131, 83, 117]

The normal resting pulmonary blood volume has been determined to be approximately 650 cc per square meter of body surface area or about 20 to 25 per cent of the total blood volume [illegible, illegible, 117] In conditions of generalized heart failure the intrathoracic blood volume may be greatly increased [26, 1 1, 83] Most of this increased blood may be stored in the enlarged cardiac chambers rather than in the pulmonary vessels [153, 77] There is disagreement as to the pulmonary blood volume in left heart failure,[1 5] Kattus et al [127] have reported normal or diminished central ' or pulmonary blood volume in patients with mitral and aortic stenosis and left sided heart failure On the other hand Borden and associates found the central blood volume increased in left ventricular failure but normal in mitral stenosis with pulmonary hypertension [illegible]

THE CIRCULATING BLOOD VOLUME IN CONGESTIVE HEART FAILURE (See p 166)

BODY WATER

Total Body Water

The general belief has been that *total body water* forms about 70 per cent of the body weight 50 per cent consisting of intracellular fluid and 20 per cent of extracellular fluid More recent determinations by the dilution of deuterium oxide (heavy water)[184] and of antipyrine[19, illegible] and N acetyl 4 amino antipyrine[11] have shown that total body water averages about 55 per cent in males and somewhat less in females [illegible] With improved methods for assaying tritium (radioactive hydrogen H^3) by means of the ionization chamber or proportional counter tritium labeled water has also been used to determine body water and has yielded results essentially similar to that obtained with deuterium and 2 to 4 per cent higher than that obtained with antipyrine [171] In edematous patients the antipyrine space has been found to be about 15 per cent smaller than the deuterium space [111] In normal persons two to four hours are required for complete mixing But in congestive heart failure and other edematous states and especially in the presence of serous effusions five to nine hours or longer may be necessary and the results are less reliable The dilution methods using radioactive materials as test substances are most accurate but involve formidable techniques Antipyrine has been found most satisfactory for clinical use but serial samples of blood are required because of its relatively rapid disappearance from the blood

The percentage of body weight due to water varies considerably with variations in body fat Determinations on the basis of desiccation studies[146] and specific gravity indicate that the body water forms a more constant percentage of lean body mass i e body weight exclusive of adipose tissue namely about 70 to 73 per cent [277, 10]

$$\% \text{ Body water} = 0.73\,(100\% - \%\text{ body fat})$$

Body fat may be determined from the whole body specific gravity[173] by the following formula

$$\% \text{ Fat} = 100 \times \frac{5.548}{\text{Sp. Gravity}} - 5.044$$

The significance of total body water in various states would be greatly enhanced if there were a simple method of assessing body fat and thereby of determining body water in terms of lean body mass

Extracellular Fluid Volume

The term *extracellular fluid volume* requires careful definition when discussed in terms of the substances used to measure it The extracellular fluid includes the plasma and the ultrafiltrate of plasma bounded by capillary and cell membranes This properly includes the extracellular fluid of bone and tendon, which has special features Many of the substances employed to determine extracellular fluid enter cells, tendon or bone to a variable extent and therefore measure a space of distribution of their own which is variably larger than the extracellular fluid volume as defined above There is no general agreement as to the inclusion of cerebrospinal fluid and gastrointestinal fluid (transcellular fluid) in the extracellular fluid

The extracellular volume has been measured by injecting known amounts of substances which are thought to mix uniformly throughout the extracellular fluid The extracellular fluid is calculated as the quantity of substance introduced intravenously divided by the concentration in the plasma at the time of complete uniform mixing Smaller spaces approximately 15 to 20 per cent of body weight, have been determined by the use of inulin[1,4,79,188] sucrose[61] mannitol[illegible] thiosulfate[33] *and radiosulfate*[illegible] *than by thio*cyanate[45] [illegible] bromide[illegible] radioactive chloride[05] or sodium Na[4,21] which yield spaces approximately 20 to 30 per cent of body weight

Studies by Swan and associates[200] of the extracellular volume in nephrectomized dogs indicated that the radiosulfate thiosulfate and mannitol volumes were apparently equal when measured simultaneously in the same animal, whereas the volumes of distribution of *inulin* and *sucrose* were somewhat smaller On the basis of simultaneous studies of the distribution of inulin and thiosulfate in tissues, and their correlation with chloride and connective tissue content of tissues in dogs Nichols and associates[157] found evidence indicating that the extracellular fluid consists of two phases (1) a smaller physiologically active space measured by inulin, and (2) a larger or total extracellular phase which includes also connective tissue extracellular *fluid, measured by substances such as chlo*ride The lowest extracellular volumes, measured by inulin, result from slow and incomplete penetration of connective tissue such as tendon Slightly higher values are afforded by substances such as thiosulfate, which penetrate connective tissue more readily or are destroyed in the body during the test period The largest "extracellular volumes" are afforded by chloride thiocyanate or sodium because they penetrate connective tissue more rapidly, because sodium in particular penetrates bone and because all three enter the intracellular space to a variable extent[140]

The imperfections in determining the extracellular fluid in normal subjects are increased in the presence of heart failure with edema and serous effusions chiefly because of the longer period required to obtain uniform mixing[illegible] Direct measurements made by the above methods as well as balance studies indicate that the extracellular fluid volume in *heart failure is two to three times the normal,* amounting to 35 to 60 per cent of body weight[1,2,216]

Intracellular Fluid Volume

Intracellular fluid is calculated as the difference between total body fluid measured as the antipyrine or deuterium space, and the extracellular fluid measured as the inulin sucrose thiosulfate or thiocyanate space[illegible] This indirect method of calculation is limited in accuracy by the imperfections in determin*ing total and extracellular body water Simul*taneous measurements by antipyrine and sucrose have indicated that the intracellular water averaged 40 per cent of body weight[197,12]

EXTRACELLULAR AND INTRACELLULAR ELECTROLYTES

This subject has been discussed in part in relation to congestive heart failure (p 168)

Extracellular Sodium and Potassium

The determination of plasma sodium and plasma potassium has been greatly facilitated by the development of the flame photometer[97] Small samples of plasma (0.5 ml), diluted 200 times for sodium and 50 times for potassium are poured into a funnel type atomizer and vaporized under constant air pressure into a flame supplied by gas under constant

exchangeable sodium, during the period of equilibrium of injected Na^{24} [59] The importance of bone sodium is indicated by evidence that about 30 per cent of body sodium is in bone (p 170)

Chlorides

The chloride concentration in plasma or urine is determined by standard chemical methods such as the modification of Sendroy's iodometric titration method[97] or that of Schales and Schales[183] Since injected bromide distributes itself throughout the body in proportion to the quantity of chloride in the body the extent of bromide dilution is used as an approximate measure of *total body chloride*[218, 65] The total body chloride is calculated by multiplying the bromide space $\left(\frac{\text{retained bromide}}{\text{plasma bromide conc}}\right)$ and the plasma chloride concentration The "chloride space" and total exchangeable chloride have also been determined by the use of radiochloride Cl^{38} [95] in a manner similar to that described for Na^{24} Intracellular chloride may be calculated by subtracting extracellular chloride (inulin or sucrose extracellular space multiplied by plasma chloride concentration) from total body chloride Then intracellular chloride concentration is determined from intracellular chloride and intracellular body water

The plasma concentration of chloride is approximately 103 milliequivalents per liter (range 90 to 110) Total body chloride averages 30 milliequivalents per kg body weight[65] *Intracellular chloride averages 25 milliequivalents per liter of intracellular fluid* This is

$$pH = pK + \log \frac{BHCO_3}{H_2CO_3} = pK + \log \frac{CO_2 - 0.1316\ \alpha\ p}{0.1316\ \alpha\ p}$$

$$= 6.10 + \frac{\log CO_2 - 0.067p}{067p}$$

substantially less than the intracellular concentration of sodium (40 mEq/L) determined by isotopic dilution There is also an excess of bone sodium over bone chloride The relatively high intracellular concentration of chloride indicates that the volume of *distribution of chloride is not an accurate* measure of the extracellular fluid

BLOOD pH AND BLOOD GASES

Studies of the blood pH, carbon dioxide and oxygen are often useful or essential in the understanding of electrolyte and hypoxic aberrations in heart failure in congenital heart disease and especially in heart disease associated with pulmonary or renal insufficiency Determinations of arterial and mixed venous oxygen concentrations are used in determining the cardiac output by the direct Fick method

Blood pH

The pH of the blood is not infrequently modified in cardiac patients with heart failure by therapeutic agents or by complicating or associated pulmonary, renal or metabolic disease The pH of plasma and of whole blood are the same The pH of the blood may be determined electrometrically, using a *Cambridge pH meter with a closed glass electrode*[139] If pH readings are not made at 37° C, a temperature correction must be made[179] In all blood gas and pH determinations the blood must be drawn without stasis and handled under anaerobic precautions to prevent loss of carbon dioxide or access of oxygen *Lactic acid formation by glycolysis must* be minimized by the use of fluoride and prompt analysis

The plasma or blood pH may also be determined colorimetrically by using Hastings and Sendroy's modification[102] of Cullen's method[47] *The whole blood or plasma is* diluted with phenol red indicator in saline and compared with standard solutions of known pH containing the same indicator

The plasma pH may be calculated from the carbon dioxide content of plasma (CO_2) the carbon dioxide tension (p) and the carbon dioxide solubility α by means of the Henderson Hasselbalch equation[210]

if CO_2 content is expressed as volumes per cent In practice the carbon dioxide content is determined and the pH of the plasma can be read directly from carbon dioxide absorption curves with plasma carbon dioxide contents interpolated on them[61, 168]

The mean pH of normal arterial blood or plasma is approximately 7 40 with a range of 7 34 to 7 43 The pH of venous blood is somewhat lower approximately 7 37, with a usual range between 7 32 and 7 41 In heart failure the arterial blood pH is usually normal or slightly elevated[7] the latter owing to alka

losis caused by hyperventilation The venous blood pH is usually normal in heart failure [191]

Acidosis, with reduction in blood pH, may occur in heart failure when there is associated renal insufficiency or carbon dioxide retention due to pulmonary insufficiency or a low plasma sodium or ammonium chloride toxicity (p 284) Alkalosis with elevated pH may occur as a result of hyperventilation of heart failure itself or associated pulmonary fibrosis with alveolar-capillary block or following vigorous mercurial diuresis

Table 6 pH Carbon Dioxide and Oxygen in Arterial and Venous Blood and Plasma

	ARTERIAL		VENOUS	
	Whole Blood	Plasma	Whole Blood	Plasma
CO_2 content m mol/l	21–22	25–27	22–24	26–28
CO_2 tension mm Hg	38–41	38–41	44–48	44–48
pH	7 40	7 40	7 37	7 37
O_2 saturation %	96–98	96 98	65–75	65–75
O_2 tension mm. Hg	95–105	95–105	33–40	33–40

Carbon Dioxide Content and Tension

Total carbon dioxide in blood includes that present as bicarbonate and that in carbonic acid The carbon dioxide content of plasma or whole blood may be determined by the method of Van Slyke and Neill [208, 168] using the manometric Van Slyke apparatus or by the gasometric method of Scholander et al [183] But this involves some difficulty in the prompt and careful anaerobic separation and handling of the plasma The *whole blood carbon dioxide content* may be measured by the manometer or in the Roughton-Scholander syringe by the combined method for carbon dioxide and oxygen [208, 183]

In normal blood the plasma carbon dioxide content is about 1 [illegible] times the carbon dioxide content of red blood cells Therefore the carbon dioxide content of plasma is higher than that of whole blood If plasma cannot be separated anaerobically the plasma carbon dioxide can be determined from line charts based on measurements of the total blood carbon dioxide oxygen capacity and pH [209]

The carbon dioxide content of arterial whole blood is approximately 21 to 22 millimols per liter, that of arterial plasma 25 to 27 millimols per liter that of venous whole blood 22 to 24 millimols per liter, that of venous plasma 26 to 28 millimols per liter

The *carbon dioxide tension* may be calculated from line charts if the carbon dioxide content oxygen capacity and pH of blood have been first determined [167] For direct determination of blood carbon dioxide tension whole blood at 37 C is equilibrated with a bubble of gas at atmospheric pressure whereby the bubble attains the same carbon dioxide tension as blood This final carbon dioxide tension of the bubble (and therefore of the blood) is determined by micro gas analysis of the bubble with the Van Slyke apparatus [210] or in the capillary portion of the same Roughton-Scholander syringe in which equilibration was effected [175, 127, 68] The *normal carbon dioxide tension* of arterial blood is approximately 40 mm Hg (usually 38 to 41 mm), and of venous blood usually 44 to 48 mm Hg The carbon dioxide tension of plasma is the same as that of whole blood The carbon dioxide content and tension of arterial whole blood are usually normal or slightly lowered in heart failure [74, 180] The venous blood carbon dioxide tension is usually normal in heart failure [180]

Oxygen in the Blood

The *oxygen content of blood* is determined by the method of Van Slyke and Neill [208] by use of Van Slyke s manometric apparatus or by the microgasometric method of Scholander et al [183] The oxygen and carbon dioxide content of whole blood can be measured simultaneously on the same specimen Arterial or arterialized blood is used This must be collected carefully without stasis or bubbles without exposure to air into a syringe rinsed with heparin as an anticoagulant and fluoride to minimize glycolysis The syringe is tightly capped and placed in a container of ice and water except when samples are removed for analysis When mixed venous blood is to be analyzed as in determining the cardiac output (p 210) it is obtained by cardiac catheterization from the pulmonary artery or right ventricle

The *oxygen capacity* is determined by first saturating the blood with air by rotating it in a separatory funnel to convert all the reduced hemoglobin to oxyhemoglobin

The oxygen saturation per cent is calculated

from the oxygen content and oxygen capacity

$$\% \text{ oxygen saturation} = \frac{\text{oxygen content}}{\text{oxygen capacity}} \times 100$$

The oxygen capacity and oxygen content, as usually determined by gasometric methods include oxygen dissolved in plasma as well as oxygen in oxyhemoglobin Therefore, to determine oxygen saturation from the content and capacity it is necessary to subtract 0 2 to 0 3 volume per cent of dissolved oxygen from the measured oxygen content and 0 5 to 0 7 volume per cent from the measured capacity the exact value varying according to the barometric pressure and room temperature of the air used to saturate the drawn blood with oxygen

Methods have been devised for more direct determination of oxygen saturation [12] to permit more rapid or continuous measurements These include the use of filter photometers (oximeters[41]) which may be attached to the warmed ear or which measure the oxygen saturation of arterial blood diverted into polythene tubing Since oxyhemoglobin absorbs less visible red light (wave length 620 to 770 millimicrons) than does reduced hemoglobin varying percentages of oxyhemoglobin and reduced hemoglobin alter the amount of light absorption and thereby the intensity of the current of the photocells in the oximeter In some oximeters the galvanometer must be preset and relative changes in oxygen saturation are recorded in others *absolute* oxygen saturations may be recorded without presetting [2,6] but the oximeter must first be calibrated against known arterial oxygen saturations Oxygen saturation of blood may be determined accurately also on undiluted, unexposed blood by direct measurement in a polarization spectrophotometer [54]

The *normal oxygen capacity* of blood varies with the total hemoglobin content Since 1 gm of hemoglobin can combine with 1 34 volumes of oxygen, blood with a total hemoglobin of 15 gm per 100 ml has an oxygen capacity of 20 volumes per cent The *normal oxygen saturation* of arterial blood is usually 96 to 98 per cent i e 96 to 98 per cent of the total hemoglobin is in the form of oxyhemoglobin

The oxygen saturation of peripheral venous blood is very variable (25 to 90 per cent) depending on blood flow and local metabolism Mixed venous blood obtained preferably from the pulmonary artery, usually contains 4 to 5 5 volumes per cent less oxygen than arterial blood, its oxygen saturation is usually 65 to 75 per cent

The *arterial oxygen tension* (pO_2) rather than its oxygen content or saturation is the factor determining the supply of oxygen to tissues and the transfer of oxygen from pulmonary alveoli to pulmonary capillaries

The oxygen saturation of hemoglobin at a constant temperature and pH is determined by the oxygen tension to which blood is exposed By plotting oxygen tensions along the abscissa and percentage of oxygen saturation on the ordinate an oxyhemoglobin dissociation curve is constructed for a given pH (Fig 56) Thus the oxygen tension of arterial blood can be read off this curve if the pH and the per cent oxygen saturation have been determined [40] The normal arterial oxygen tension is 95 to 105 mm Hg at sea level

The nature of the curve is such that reliable oxygen tension values are obtained for oxygen saturations between 10 and 70 per cent where the curve is virtually linear Above 70 per cent oxygen saturation the curve tends to level off and then flattens to such a degree that slight changes in oxygen saturation correspond to relatively large changes in oxygen tension A fall from 98 to 95 per cent arterial oxygen saturation corresponds to a fall of pO from about 100 to 80 mm Hg and at 90 per cent oxygen saturation the oxygen tension of arterial blood at pH 7 4 is approximately 60 mm Hg Hence slight errors in the determination of oxygen saturation in its higher ranges may result in significant errors in pO_2 when the latter is calculated from the oxyhemoglobin dissociation curve

The nature of the dissociation curve in the higher ranges of oxygen saturation is important in the interpretation of even slight reductions on oxygen saturations found in some cases of heart failure or pulmonary disease Thus an arterial oxygen saturation of 93 per cent sometimes regarded as virtually normal actually represents only 70 to 75 mm Hg oxygen tension instead of the normal of about 100 mm Hg

For more accurate determinations of arterial oxygen tension, the blood sample is equilibrated by thorough mixing with a small bubble of a gas in a closed tonometer or

syringe[175, 84] The gas bubble attains the same tension as the gas tension of the blood. The oxygen content of the bubble is determined by the Van Slyke manometric apparatus or in the Roughton-Scholander syringe in which equilibration of the blood and gas bubble is performed. The final oxygen tension of the bubble is calculated from its oxygen content and this tension is presumed to be identical with the oxygen tension in the drawn blood. Accuracy in this difficult method depends on avoidance of errors in blood sampling, in metabolism of the blood, and in analytic technique.[33, 83]

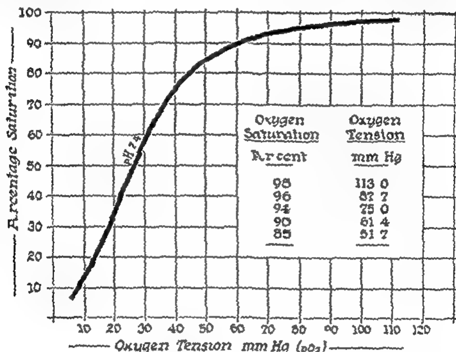


Fig. 56. Oxygen dissociation curve—human blood.

Another method particularly applicable to oxygen tensions in the high range (above 150 mm Hg) depends on measurements of the concentration of physically dissolved oxygen made on plasma separated anaerobically from erythrocytes. These measurements may be made by gasometric analysis or by polarography.[10]

TEST OF PULMONARY FUNCTION (see p. 971)

TESTS OF MYOCARDIAL RESERVE

In most cases of cardiac *disease* without failure, tests of circulatory *function* may all yield normal results. This merely indicates that the circulatory compensations for the disease are adequate to maintain a normal circulation when the patient is at rest or performing his ordinary activities. Additional tests have been designed to determine the adequacy of the circulatory response when some special strain is placed on the circulatory system. These are really attempts to test the myocardial reserve (p. 87).

Tests of myocardial reserve[150, 13, 1, 68] usually note the effect on the pulse rate, the blood pressure or the respiratory rate after the patient performs some procedure which strains the circulation. Most often this strain is effected by some form of physical exercise, but breath holding, the Valsalva procedure, immersion in warm bath, and others have also been employed. In addition to observing the effect on the pulse, blood pressure or respiration, one may also study the effect on the electrocardiogram, the size of the heart or the consumption of oxygen.[161]

A commonly used simple test consists of recording the pulse rate before and after the subject changes from the sitting to the standing position, after 10 knee bendings or after hopping 50 times on one foot. If the original pulse rate is 80 per minute, the increase in

rate should not exceed 10 on standing 20 after knee bending or 30 after hopping In each of the tests the pulse rate should return to the original level within two minutes As a result of the test the blood pressure should not rise more than 10 mm Hg and should return to the initial level within two minutes The respiratory rate should not increase more than 6 per minute Messinger[143] has stressed the value of observing the ratio of the pulse rate to the respiratory rate In normal subjects this ratio increases with exercise in patients with cardiac disease it does not increase Thus the ratio after an exercise test in normal persons was found to be 5 5 but in cardiac patients it was less than 4 5

Efforts have been made to standardize these exercise tests so that a fixed amount of exercise is performed in a given time, the amount depending on the age sex and weight of the subjects Such a standardized exercise tolerance test involving a variable number of ascents of two steps each 9 inches high, in a period of one and a half minutes was described by Master and Enid Oppenheimer[141] The number of climbs for each subject is determined from tables In normal persons *the pulse rate does not rise more than 10 beats* per second and the blood pressure not more than 10 mm Hg Both return to the initial level in two minutes

The clinical history is often a better guide to the patient s response to exercise than any of the utilized objective tests The amount of activity required to produce dyspnea and any change in the ability to perform usual activities without dyspnea are often revealing as to the maintenance or reduction of normal cardiac function Due care is required in the interpretation of dyspnea and its differentiation from sighing respiration The possible role of pulmonary disease obstructive diseases of the respiratory tract recent excessive weight gain and obesity requires careful study

A variety of other tests of myocardial reserve have been described One of the simplest is the *breath holding test* The normal person can hold his breath for 30 seconds or longer Subjects with limited cardiac reserve cannot usually do this for more than 20 seconds The same test may be performed immediately after some exertion such as 10 knee bendings After such exercise the patient with diminished cardiac reserve cannot usually hold his breath for more than 12 seconds A modification of this test consists in observation of changes in the pulse and blood pressure while the subject is blowing through a tube against a fixed pressure A clinical instrument of this type, termed the Flanmeter, has been used to test circulatory fitness[210] The *Schellong test* requires a subject to stand for ten to twenty minutes during which time continuous measurements of his blood pressure are recorded Poor circulatory function is denoted by a fall of the systolic blood pressure of 20 mm Hg or more The subject may collapse if the fall in pressure is excessive especially if he suffers from postural hypotension

During the *Valsalva test*, the heart in normal persons becomes smaller, as observed by fluoroscopy In patients with poor myocardial reserve it may dilate Electrocardiographic studies following exercise have also been utilized to demonstrate poor myocardial or coronary circulatory reserve (p 469) Similar electrocardiographic changes are produced by breathing procedures associated with anoxemia (Chapter 18)

Nylin[161] utilized the determination of the oxygen debt after exercise as the basis of a test of circulatory function After a standard exercise which consists of stair climbing Nylin observed that the increase in oxygen consumption after cessation of exercise (i e the oxygen debt) is much greater in subjects with diseased hearts than in normal persons A diminished capacity in cardiac patients for increasing the cardiac output during exercise is the basis of a cardiac function test utilized by Neukirch[155] A diminished capacity of cardiac patients to increase oxygen consumption during a standard strenuous exercise test may also be used as a test Szostrand and Wahlund[92] determined the rate of work on a bicycle ergometer which caused a rise in pulse rate to 170 per minute In cardiac patients this occurred at relatively low work intensities

The various tests of circulatory function or myocardial reserve are of very limited value The responses of pulse and blood pressure to stresses are too variable to be employed as a diagnostic test and there is considerable overlapping of the findings in normals and cardiac patients Most important the response to these stresses frequently depends on emotional factors and training and may be modified also by pulmonary metabolic, muscular or cerebral disease as well as by cardiac disease

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Chapter 11

THE TREATMENT OF CONGESTIVE HEART FAILURE

Treatment of the Underlying Causes of Heart Failure

In order to treat congestive heart failure most effectively it is desirable to determine the etiologic factors responsible for its development. In many cases, e.g. those due to coronary artery disease, no specific treatment can be applied to the etiologic factor. In other cases of congestive heart failure, the major element in treatment is the cure or alleviation of the underlying cause. Thus thyroidectomy or antithyroid medication in cases of heart failure due to Graves' disease, decortication of the heart in those due to constrictive pericarditis, and closure of the fistula in those due to an arteriovenous aneurysm are often life saving measures without which treatment of heart failure per se is futile. Similarly specific medical treatment of vitamin B deficiency, hypothyroidism, anemia or diphtheria toxemia may be curative in cases of heart failure associated with beriberi heart disease, myxedema heart, chronic or acute hemorrhage or diphtheria respectively. Repair of a patent ductus arteriosus, coarctation of the aorta, or of other congenital cardiovascular defects may dispel heart failure.

When cardiac failure appears early during pregnancy, a therapeutic abortion may be necessary to alleviate the symptoms. When cardiac failure is precipitated suddenly by extreme tachycardia such as may accompany a paroxysm of atrial fibrillation, treatment consists of prompt slowing of the heart by digitalis, strophanthin or quinidine. Heart failure with pulmonary edema precipitated by a hypertensive crisis may be controlled by parenteral administration of a hypotensive drug such as protoveratrin. Mild antiluetic therapy directed against the primary cause of failure associated with syphilitic heart disease gives less striking results than in the conditions mentioned above but it may prolong life.

Preventive Measures

The prevention of cardiac failure in patients with known heart disease is pertinent. Respiratory infections should be avoided, especially in patients with rheumatic heart disease. The prophylactic and therapeutic use of antibiotics to control infections is of special value in cardiac patients. Limitation of emotional strain and physical exertion may be important in patients with hypertensive or coronary heart disease. Chronic cough should be controlled by rest, codeine, etc., as the associated strain may precipitate cardiac failure. Lesions associated with recurrent bleeding and anemia, e.g. peptic ulcer or bleeding hemorrhoids should be cured medically or surgically, especially in patients who already suffer from an insufficient coronary blood supply. The rapid or excessive intravenous administration of fluids may induce congestive heart failure and should be avoided. The adequate specific treatment of syphilis in patients with early cardiovascular syphilis will prevent or postpone the development of heart failure. Similarly control of hyperthyroidism should be effected before cardiac failure develops. Dietary control of obesity, particularly in middle-aged or elderly cardiac patients may diminish the probability of heart failure.

Prophylactic periods of bed rest are desirable for patients who have previously suffered attacks of failure. Careful maintenance of digitalization, low sodium intake and other prescribed medication are often essential to avoid recurrence of heart failure after the initial attack is controlled. Avoidance of prolonged or exaggerated bed rest and the use of anticoagulants in cardiac patients requiring bed rest may diminish the probability

of thromboembolic complications and their precipitation of heart failure

GENERAL THERAPEUTIC MEASURES

Principles of Treatment

In addition to the elimination or control of the precipitating or contributory factors treatment consists essentially of the following

1 *Improvement in cardiac efficiency* This is effected by (a) limitation of physical activity which reduces the load on the heart and (b) digitalis administration which improves cardiac function probably by direct action on the heart

2 *Control of sodium water retention* This involves a sharp limitation of sodium intake and the use of diuretics especially mercurial diuretics which promote the excretion of sodium and water through the kidneys

These and other secondary therapeutic measures will be discussed individually in the following pages However in execution most of these therapeutic measures are utilized simultaneously To obtain maximal effects as soon as possible Gold Kwit et al[148] have recommended a five pronged program including (a) rest in bed or chair (b) extreme sodium restriction (c) daily mercurial diuretics (d) single dose rapid digitalization and (e) daily weighing as a guide to the removal of extracellular fluid (edema) The program is continued until all gross signs of edema disappear and the body weight reaches a minimal and basic level Attractive as their routinized program appears great caution and judgment are essential in its application to individual patients There is danger in the simplicity of dogmatic therapeutic instructions In particular digitalis dosage and the frequency with which mercurial diuretics are administered require considerable elasticity

It is equally important to maintain therapeutic control after the manifestations of congestive heart failure have been abolished Activity is limited but liberalized according to tolerance Digitalization is maintained Sodium restriction and the administration of mercurials are continued according to the patient s weight and clinical symptoms The optimum regime should be maintained as the diabetic s regime is maintained It is as faulty to discontinue treatment until heart failure recurs as to restrict diet and administer insulin to the diabetic only when he develops diabetic acidosis However occasionally when heart failure is precipitated by an acute infection or the sudden development of severe anemia compensation is readily established by control of infection or anemia and may be maintained without continuing digitalis diuretics or a strict low sodium diet

REST

The Rationale of Rest

Rest is designed to alleviate heart failure by diminishing the work of the heart Heart failure denotes an inability to maintain an output adequate for the needs of the body Those needs can be minimized by eliminating physical exertion Hickam and Cargill[179] showed that the patient in heart failure is unable to meet the stress of exercise with an increase in cardiac output as the normal individual does Merrill and Cargill[81] found that the renal blood flow in patients with moderate heart failure may be normal with the patient at rest but inadequate with exercise And Landis et al[85] observed in experimental heart failure that the venous pressures which were normal with the animal at rest became elevated during exercise These abnormalities of renal blood flow and of venous pressure induced by activity have been related to some of the basic disturbances in heart failure (sodium water retention and edema) Activity promotes the venous return and produces pulmonary congestion and dyspnea when the left side of the heart is incompetent The purpose of bed rest is to avoid these circulatory handicaps imposed by activity

Rest reduces the work of the heart also by diminishing the blood pressure thus permitting the heart to contract against a lower resistance By eliminating dyspnea rest decreases the work of the respiratory muscles the oxygen utilization and the work of the heart By slowing the cardiac rate it prolongs the diastolic period of recovery and results in improved efficiency of cardiac contraction The final proof of the value of rest is the rapid alleviation of dyspnea and other symptoms which the patient often discovers for himself Often especially when the symptoms of failure are relatively mild and of brief duration rest alone effects a cure This was strikingly indicated by Fothergill[7] in 1872

In recent years attention has been directed repeatedly to the dangers of bed rest[164, 77, 210] These admonitions should not be misin

terpreted The physician must distinguish between essential bed rest and unnecessarily prolonged bed rest, between the judicious use and the excessive abuse of rest A distinction should be drawn also between rest and recumbency For patients with congestive heart failure may obtain the desired rest, with more comfort propped up in a large chair or bed than when at complete rest in the horizontal position If bed rest is desirable 8 to 10 inch blocks may be placed under the head posts to relieve orthopnea

The greatest danger of bed rest in patients with heart failure is the invitation to phlebothrombosis and pulmonary embolism Deep breathing and leg exercises changes in position and the use of anticoagulants are measures designed to overcome these dangers (p 572) The hazard of bronchopulmonary infections always lurking in patients with bronchial or pulmonary stasis due to congestive heart failure, is enhanced by inactivity in bed especially in the obese the indolent and the elderly The restricted judicious use of sedatives and narcotics will minimize the danger of complete immobility of the patient Exaggerated straining at stool in using a bed pan often enhances the danger of fatal pulmonary embolism

Elderly patients often become completely bedridden with prolonged bed rest Osteoporosis bone atrophy and muscle wasting become intensified Urinary retention may be precipitated in patients with prostatism Constipation, cathartic habituation, back strain bed sores and psychoneurosis are among the other hazards attributed to complete and prolonged bed rest

Duration of the Rest Period in Bed

Rest may involve a complete stay in bed for a continuous period, confinement during occasional days of the week or hours of the day or various modifications of these, or it may merely consist of a limitation of activity at work or at home These are discussed below

According to its severity, heart failure may require the patient to remain in bed for periods of one to four weeks or longer Usually in uncomplicated cases of moderate severity, proper treatment combined with such a period of minimal activity suffices to enable the heart to build up a reserve so that symptoms will not readily reappear when normal or moderately limited activity is gradually resumed On the other hand, in very severe cases or in patients with a delayed therapeutic response, bed rest may have to be prolonged The advantages of prolonged bed rest (twelve to seventy two weeks) as compared with rest for a few weeks were reported by Davis[80] in a comparative study of patients with congestive heart failure Davis emphasized that bed rest should be continued for a variable number of weeks after the disappearance of evidences of failure in order that the heart may reach an optimum capacity for work

The whole question of duration of bed rest still requires study Fixed periods cannot be prescribed for all cases of heart failure since each presents an individual problem Certainly the very long periods mentioned above are not advisable for many patients with symptoms of moderate severity which respond rapidly to simple measures When patients have only mild symptoms, such as exertional dyspnea and when economic restrictions are placed on the rest period, a period of four to seven days in bed may suffice to begin treatment The response of symptoms to rest and resumption of activity will aid in determining whether longer periods of rest are necessary

The above mentioned periods of bed rest may be prolonged not only by a poor therapeutic response but by associated diseases which precipitated failure or by complications of heart failure Patients with acute coronary occlusion and failure may have to be kept in bed for four to six weeks and sometimes for several months The patients with active rheumatic fever should remain in bed as long as there are symptoms or signs of rheumatic activity It must be emphasized that complete bed rest is not terminated merely because the patient has already spent eight twelve or even twenty weeks in bed In the final analysis the clinical course of the patient and not an arbitrary time limit is the determining factor

The resumption of some degree of exertion as soon as this can be effected without danger, serves to improve muscular tone which aids the venous return to the heart and increases general physical fitness Rest should not be prescribed at all for patients whose dyspnea is associated with neurocirculatory asthenia or anxiety neurosis Neither is rest indicated merely because of the presence of cardiac disease if this disease is well compensated On the contrary controlled physical training a

desirable in these conditions in order to enable the patient to carry on normal activities

Complete Bed Rest

Sometimes rest in bed fails to bring about a satisfactory symptomatic improvement until it is rigidly enforced and activity is absolutely proscribed Bathroom privileges trips to the telephone getting out for meals and occasional excursions out of the bedroom may completely nullify the therapeutic effect of rest in bed When heart failure is associated with coronary thrombosis active rheumatic fever or other febrile diseases or when it fails to respond to partial limitation of activity, complete bed rest must be enforced

Complete bed rest does not imply that the patient must lie flat in bed Usually he is most comfortable if his head and shoulders are propped up by two or more pillows Special beds which permit elevation or depression of the upper or lower ends are ideal for obtaining the proper elevation of the head and chest When orthopnea is intense the position of the bed should be fixed so as to place the patient in a sitting position If the bed is not adjustable the patient may sit at the side of the bed with his feet hanging onto a chair and his back and head supported by pillows or the head of the bed may be elevated by blocks Adequate rest with maximum comfort is often best attained in a large cushioned chair Patients with severe congestive heart failure usually have a remarkable capacity for finding the position best suited for their circulatory status and the physician should help them attain and maintain that position with comfort and not arbitrarily modify it

The enforced use of the bedpan is often a distortion of the purpose of bed rest Straining at stool involves the Valsalva procedure and the concomitant risk of pulmonary embolism It is obvious that many patients will profit more from permission to use the commode at the bedside or even from one daily trip to the bathroom if necessary than they risk from these slight activities Elderly patients with prostatic enlargement likewise benefit more from commode or lavatory privileges than from extreme restriction to bed Similarly leg and breathing exercises and frequent changes of position in bed by minimizing the risk of phlebothrombosis and pneumonia are desirable activities which are not incompatible with the benefits of bed rest In summary the application of rest as a therapeutic measure requires judgment and individualization in each case the advantages and disadvantages must be carefully assayed

Mental Repose

Complete bed rest is ineffective unless there is mental as well as physical repose The sick room should be quiet and the atmosphere as pleasant as possible The shades should be drawn when the patient is napping Visiting hours should be completely restricted at first and limited later The patient should not be permitted to converse excessively Upsetting visitors or long discussions should be avoided Morphine is sometimes necessary the first few days in certain forms of heart failure but later milder sedatives will suffice (see below) However the indiscriminate administration of narcotics and sedatives is dangerous Sedatives and narcotics may interfere with the action of diuretics Sleep is essential if the rest treatment is to be effective soporifics should be administered when required Psychotherapy including optimism encouragement and reassurance will increase the advantages of rest The patient should not be permitted to become depressed by the thought that going to bed is the end stage of his cardiac disease or by the fear of chronic incapacity Often it can be honestly stated that complete rest in bed is not a desperate measure of last resort but one of limited duration utilized prophylactically to prevent more serious symptoms and to build up cardiac reserve so that the patient can resume his normal or restricted activity

Modified Bed Rest

If the symptoms of heart failure are mild e g if there is dyspnea only with moderate exertion it may not be necessary or economically feasible to put the patient to bed for a continuous period Similarly after a therapeutically successful period of complete bed rest modification of the restrictions may be permitted Bed rest may then be tempered with the privilege of leaving the bed for the bathroom or for meals If the indications are less urgent the patient may be required to go to bed one or two days a week usually at the week-end Or rest periods may be prescribed each day together with early retirement each evening An hour s rest (in bed if possible) after the noonday and evening meals an afternoon nap and resting for one to two hours before going out occasional evenings are all desirable forms of partial rest for patients

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It is the sodium and not the chloride ion which is responsible Ammonium chloride and potassium chloride exert a diuretic action whereas sodium bicarbonate is as water retaining as is sodium chloride

Sodium Restriction

Recent advances in understanding the relationship of odium and water to heart failure include a much greater emphasis on extreme restriction of sodium intake and less emphasis on the value of fluid restriction The physician must clearly and specifically indicate the exact quantity of sodium permitted in the daily diet, the ordering of a low sodium or low salt diet will evoke a remarkable variation in sodium intake usually excessive and ineffective Schroeder[271] showed that limitation of sodium chloride intake to 1 0 gm a day was usually enough to cause diuresis or prevent edema But in cases of severe heart failure of long duration it was necessary to reduce the intake of salt to as little as 0 5 gm (200 mg of odium) per day As a rule the treatment of congestive heart failure should begin with a sodium chloride intake of no more than 1 0 gm daily but the subsequent course may indicate that a more liberal allowance is permissible without recurrence of evidences of heart failure On the other hand the sodium intake may have to be restricted to 200 mg or less daily if the heart failure appears to be otherwise refractory to treatment Occasionally the requirements of hunger and palatability demand a more generous sodium intake than is ideally desirable but this may be compensated by the use of diuretics just as in diabetes a patient may prefer to take insulin rather than further to restrict his food allowance A more liberal sodium intake may also become permissible if the food to be ingested can be mixed with suitable cationic exchange resins which withdraw sodium and pass through the intestinal tract without being absorbed

A sharp limitation in salt intake may be effected by first placing the patient with heart failure on the Karell[190] regime which permits nothing by mouth except 800 cc of milk daily This allows about 1 gm of sodium chloride and 550 calories daily Even less sodium is obtained if salt poor powdered milk preparations are used such as Lonalac (Mead Johnson) or the more palatable Walker Gordon low sodium milk The advantage of the Karell regime is that it is a simple, fool proof method of assuring a low sodium diet until control over the patient can be effected and a more permanent regimen instituted

After a few days low sodium diets may be prescribed with more varied foodstuffs according to the patient's needs The normal daily diet contains 10 gm of sodium chloride or more The salt intake varies between 3 and 5 gm daily if no salt is added at the table and obviously salt rich foods are excluded Further reduction to 2 to 4 gm daily is effected by omitting all salt from cooking For stricter sodium poor diets detailed care is necessary in the choice of foods

The common sources of sodium are

1 Salt added in cooking or at the table Sodium bicarbonate Bisodol and other sodium-containing medicaments Baking soda Sodium containing tooth pastes Laxatives with sodium (e g sodium phosphates) Celery salt Garlic salt
2 Bread crackers pancakes salt-containing ready to-serve cereals cakes spaghetti, macaroni
3 Milk cheese salt butter margarine and sour cream
4 Smoked and salt cured meats and fish including ham bacon salt pork corned meats canned meats and fish shell fish sausages herring delicatessen meats clams crab heart kidney brains, lobster shrimp anchovies caviar
5 Bouillon and meat extracts used in soup Beer Pepsi cola
6 Canned vegetables soups Canned or frozen foods with sodium benzoate added
7 Spices and condiments including olives pickles catsup mustard sauces salad dressings relishes raisins dried figs
8 Pretzels popcorn salted nuts potato chips most candies and candy bars
9 Beets celery kale, lima beans sauer kraut spinach

Foods permitted in a low sodium diet include

1 Fresh fruits (raw or cooked) and fruit juices canned dried or frozen fruits or juices (unless label states that salt or sodium benzoate has been added)
2 Fresh or frozen green vegetables without salt Frozen peas are sometimes salted The following vegetables are usually permitted

Asparagus	Cucumber	Parsnips
Beans	Eggplant	Peas
Broccoli	Endive	Pumpkin
Brussels sprouts	Lentils	Radishes
Cabbage	Lettuce	Squash
Carrots	Mushrooms	Tomatoes
Cauliflower	Onions	Turnips
Corn	Parsley	Watercress

3 Potatoes rice cooked cereals prepared without salt Among the prepared cereals Puffed rice puffed wheat shredded wheat Barley Cream of Wheat, farina, hominy, macaroni, oatmeal

4 Passover bread (matzoth), special bread prepared with yeast but without salt and baking powder

5 Butter—only if unsalted olive oil and other vegetable oils shortening Spry, Crisco lard

6 Milk—limit to two glasses of dialyzed milk (Lonalac) Ordinary milk is relatively rich in sodium Unsalted cottage cheese

7 Meat fish or poultry prepared without salt, is moderately rich in sodium and should be limited to 3 or 4 ounces The following are usually permitted in low sodium diets chicken, turkey, lean beef (hamburger steak, roast beef, stew), lamb chops roast lamb, lamb stew, liver roast pork and pork chop, roast veal and veal chop, fresh fish (bass, cod, halibut oyster perch salmon, trout)

8 Egg—limit to one daily

9 Desserts and spreads Custards, junket, plain puddings using milk and egg from above allowance fruit pies with unsalted crust Jello jams jellies, marmalade, honey, sugar maple syrup, molasses ice cream prepared without salt unsalted nuts, sherbet, cakes cookies, muffins and fruit pies prepared with low sodium baking powder and without added salt

10 Beverages Tea coffee, carbonated drinks fruit juices ginger ale grape juice Coca cola lemonade Unsalted cream soups

Drinking water contains a minimal sodium content except in a few cities or in places where water softening equipment is used For very low sodium diets the sodium content of drinking water should be checked by inquiry from state or municipal laboratories The sodium content of the public water supply in certain cities has been analyzed and reported by Bills et al[29]

Palatability may be increased by seasoning with onions, pepper, lemon vinegar, curry, mint, mustard, caraway paprika sage garlic pimento, or by flavoring with cocoa chocolate, coffee caramel, maple peppermint, lemon, orange vanilla, cherries, cloves cinnamon, nutmeg ginger, salt poor mayonnaise, salt poor French dressing

Potassium chloride is sometimes substituted for sodium chloride as in Neocurtasal (Winthrop) This is acceptable to some patients but is somewhat bitter and unsatisfactory for most While Neocurtasal contains substantial amounts of ammonium chloride as well as small amounts of potassium and calcium formate and magnesium citrate, Diasal is essentially potassium chloride with a trace of glutamic acid[274] It appears to be the most generally preferred sodium chloride substitute both for addition to prepared food and for use in cooking Co salt resembles Neocurtasal in its potassium and ammonium chloride contents but also contains small amounts of calcium phosphate and choline Gustamate contains monoammonium glutamate glycine and glutamic acid Patients often complain of its after taste In the presence of associated renal insufficiency potassium salts should not be administered because of the risk of inducing toxic effects or death from hyperkalemia Lithium salts, used as sodium substitutes to improve palatability have been reported to cause serious toxic manifestations and fatalities [illegible][16]

When the sodium intake must be stringently reduced to no more than 200 mg sodium daily it is necessary that the physician be familiar with the sodium content of all of the more common foods which may be taken by the patient The regular white and rye breads contain about 170 mg sodium per slice (ounce) It is apparently extremely difficult or virtually impossible to formulate a reasonable 200 mg sodium diet (500 mg sodium chloride) and permit the use of regular bread An 8 ounce glass of milk contains 125 mg sodium and an ounce of cream 10 to 15 mg There are 40 mg of sodium in an egg and 15 to 25 mg sodium per ounce of most forms of poultry, fish or meat White meat of poultry has less sodium than dark meat

In planning a low sodium diet[330] the following list and quantities may be used to formulate a basic 200 mg diet The proper caloric allowance is then obtained by adding the

desired amount of salt free bread or cakes potatoes rice spaghetti noodles and fats Increases in sodium allowance can be obtained by substituting variable quantities of regular milk for low sodium milk (Lonalac) regular bread for salt free bread or additional meat or egg Even more rigid sodium restriction is represented by the Kempner diet (p 935) which consists entirely of rice fruit fruit juices sugar and vitamin supplement *and contains 100 to 150 mg (4 1 to 6 5 mEq)* of sodium Sometimes the effectiveness of rigid sodium restriction in heart failure is not demonstrated until the patient is placed on the Kempner diet partly because he is less apt to err in his dietary intake when the latter is so rigorously simplified

At best, very low sodium diets are unpalatable monotonous and difficult for most patients to follow for extended periods of time For this reason every effort must be exerted to make the food as attractive as possible by careful attention to variety in the choice of foods to the liberal use of permitted spices and herbs to the use of salt substitutes to home-made preparation or purchase of bread cakes candies of low sodium content *and to attractiveness in serving the* food A number of leaflets manuals and cookbooks have been published which aid in the planning and preparing of low sodium meals [144 372 377 380]

The value of restricting sodium seems apparent in patients with anasarca and serous

Table 7 Basic 200 mg Sodium Diet

FOOD	QUANTITY PER DAY	SODIUM CONTENT mg
Meat poultry or unsalted fish	5 oz cooked	100 125
Egg	1	40
Vegetable (see those permitted above)	3 avg portions (300 gm)	25
Fruit	4 average portions	8
Lonalac milk	1 pint	10
Fats	20 gm	1
Salt-free bread or salt free matzos or cereal	according to caloric need	
Rice noodles potato	1 serving	
Salad with saltless dressing		
Beverage	3 servings	
Sugar		
Jelly		

To increase the above to 500 mg sodium daily one may increase the meat or egg allowance or add regular milk (125 mg per 8 oz glass) or one may permit one or more slices of regular bread (170 mg sodium per slice) or combinations of these Thus 1 glass of regular milk and 1 slice of regular bread would increase the above 200 mg diet to a 500 mg diet

To increase to a 1 gm sodium (2 5 gm sodium chloride) daily intake one pint of milk (250 mg sodium) 3 slices of regular bread (500 mg sodium) 6 oz of meat poultry or fresh fish (120 mg sodium) 2 eggs (80 mg) may be taken in addition to permitted fruit vegetables cereals fats etc provided that no salt is used in cooking or at the table The quantities of fats starchy vegetables salt free or regular bread permitted will be determined by the desired total caloric intake but with due regard for the sodium allowed

effusions Such restriction is believed to interfere with the transudation of fluid from the blood stream into the tissues it may actually cause a reversal of flow and diuresis It is equally important to recognize the benefits of salt restriction in patients with left sided heart failure who have no obvious edema Attacks of nocturnal dyspnea and cough or of pulmonary edema may be prevented by sodium restriction In some nonedematous patients with congestive heart failure the presence of extensive occult edema is sometimes indicated by a sharp diuresis and the loss of 5 to 10 pounds in weight when fluids and salt are restricted usually in combination with other therapeutic measures

Patients vary greatly in their tolerance of salt restriction Many become habituated to rigid limitation of salt and suffer no discomfort whether or not substitutes are used Others react badly with even mild depriva

tion Occasionally the limitation of sodium together with its excessive elimination due to powerful diuretics leads to severe electrolyte disturbances in the blood and serious clinical manifestations (p 275) It may be necessary to increase the sodium allowance in such cases In some patients extreme sodium restriction and vigorous mercurial diuresis diminish glomerular filtration and further enhance the renal impairment of sodium water excretion However, the risks involved are relatively rare and minimal compared to the advantages that have accrued from the use of the mercurial diuretics and very low sodium diets These dangers should not be exaggerated lest many patients with heart failure be deprived of the two therapeutic measures which represent our greatest advance in the past twenty five years in the treatment of this condition

Fluid Intake

It has long been the practice to restrict the intake of water by patients suffering from congestive heart failure especially in the presence of edema Yet recent evidence indicates there is usually no primary impairment in the excretion of water However the cardiac patient who is unable to excrete sodium properly and has a positive balance with respect to this ion will also retain fluid in sufficient quantity to keep his extracellular fluid isotonic In fact when sodium intake is restricted to minimal levels the ingestion of plain water even in large amounts may actually augment diuresis and diminish edema in some cases

Recent studies by Schroeder[287] Schemm,[291] Bridges et al [] Leevy et al [207] and Gorham and his associates[151] have demonstrated the effectiveness of *very low* sodium intake in cardiac failure if at the same time water intake was not restricted When the diet contained less than 1 gm of sodium chloride daily Schroeder observed an occasional increase in diuresis when the patient took generous quantities of fluid and a diminution when fluids were rigidly restricted Schemm employed a diet containing less than 2 0 gm daily and claimed beneficial results from forcing fluids to 5000 cc and over daily

Gorham et al [151] observed that with low sodium diets the net loss of sodium and edema was greater when patients were *encouraged* to take 3000 cc of fluid daily than when they were restricted to 1500 cc, but little added benefit accompanied the forcing of fluids above 3000 cc Gorham et al suggested that the fundamental object was the maintenance of a low sodium intake relative to the water intake rather than a low sodium or high water intake per se, because of the dehydrating effect of hypotonic salt solution Studies by Crutchfield and Wood[73] of urine volume and total renal sodium excretion during water diuresis disclosed that water diuresis per se increased sodium excretion if the urinary output was previously low But water diuresis diminished the sodium excretion if the previous urinary volume exceeded 2 to 3 liters daily These studies suggest that maximal sodium excretion and urinary output can be obtained in most patients with heart failure on a given sodium allowance when the water intake is between 2 and 3 liters daily

Studies with water loads indicate that as a rule cardiac patients respond with a diuresis after about 50 to 60 minutes as normal individuals do But the quantitative response is often below normal The reduction in diuretic response may be striking in patients with congestive heart failure In some patients with very severe heart failure and marked edema the administration of a water load may result in water retention Abnormal retention of ingested water is particularly common in patients with so called refractory heart failure Whether this water retention is entirely secondary to extreme sodium retention or whether there is an independent antidiuresis of water in severe heart failure is uncertain Because of this abnormality in excretion of water I have come to restrict the intake of *fluids as well as sodium* in those patients who appear to suffer from intractable heart failure and whose plasma sodium is greatly diminished (p 275)

Diet

Except for the restriction of salt, the diet is not usually a major element in the treatment of congestive heart failure The two main principles to be followed when there is no contrary indication are (1) low caloric intake and (2) small, *frequent feedings* Otherwise the general rules of dietetics are followed Often the diet is determined by associated conditions such as fever, obesity or malnutrition avitaminosis anemia diabetes

The benefits of a low caloric diet result from its reduction of the work of the heart This is due to the fact, demonstrated by Proger and

Magendantz[267] that dietary restriction causes a sharp decrease in the basal metabolic rate and a significant lowering of the cardiac output the blood pressure and the heart rate At the same time the patient s vital capacity is increased and he is able to perform more work Low caloric diets are especially indicated in obese patients with hypertensive and coronary heart disease—particularly when they are confined to bed by symptoms of heart failure On the other hand children with cardiac failure and active rheumatic carditis are usually undernourished as are often patients with cardiac failure secondary to avitaminosis and those with advanced right sided heart failure Dietary restriction may be unwarranted or deleterious in such cases In some cases of heart failure especially those due to constrictive pericarditis hypoproteinemia may be severe A high protein intake appears desirable in such cases Patients with diabetes and coronary heart disease who require insulin therapy should receive an adequate carbohydrate allowance in order to avoid anginal pain due to hypoglycemia (insulin shock)

The total food intake should be divided so as to give small *frequent feedings* (five to six times daily) This avoids excessive gastric filling with consequent abdominal distention elevation of the diaphragm and diminution in vital capacity Patients who suffer from nocturnal dyspnea cough or pulmonary edema should take neither food nor fluids after an early evening meal

The *vitamin content* of the diet should be adequate or supplemented by vitamin concentrates In particular vitamin B should be added to the diet by giving thiamine chloride 5 to 10 mg daily in divided doses and brewers yeast 4 tablets three times daily When there is reason to suspect a vitamin B_1 deficiency as a prime or contributing cause of the failure 20 to 100 mg of thiamine chloride should be given daily parenterally followed after a brief interval by 10 to 20 mg daily by mouth Recently there has been interest in the occurrence of thiamine deficiency as a result rather than a cause of congestive heart failure Anorexia due to venous congestion of the gastrointestinal tract or cardiac drugs hepatic dysfunction and the prolonged use of diuretics are factors in heart failure which may lead to thiamine deficiency[257] This is especially important since cocarboxylase derived from thiamine is required for utilization of pyruvate by the heart muscle Protein and niacin deficiencies often accompany a deficiency of thiamine chloride and these should likewise be corrected

Palatability of the diet is extremely important This should be attained by care in the preparation and serving of the food and a choice as far as feasible from among those foods which the patient prefers and knows he can tolerate Usually a *bland, low residue* diet is better tolerated than one with considerable roughage since the latter tends to cause distention and flatulence Cheeses cabbage Brussels sprouts and other members of the cabbage family chocolates nuts pastries gravies fried foods and charged waters should be avoided because of their tendency to cause distention and flatulence Most patient do not tolerate raw fruits or large quantities of fruit juices which may cause not only distention but also heartburn and other symptoms of gastric hyperacidity or pylorospasm Milk should be excluded if it is not well tolerated

Alcohol There is no specific objection to the ingestion of moderate quantities of alcohol except in so far as it adds to the caloric intake *Small amounts* of sherry whiskey or brandy are often of benefit especially to the aged to those suffering anorexia and weakness and to patients with coronary artery disease and angina pectoris But alcohol is detrimental to patients with associated peptic ulcer or gastric hyperacidity with irritable colon or colitis or with prostatism

Tobacco There is no clear evidence of harm from smoking so far as heart failure itself is concerned but as a rule dyspnea and especially cough due to left sided heart failure are intensified by smoking If it is too difficult to discontinue the habit moderate smoking (5 cigarettes or less or 2 cigars daily) is permissible provided no unfavorable symptoms are produced However if palpitation or extrasystoles occur if there are heartburn and other evidences of gastric distress cardiac or epigastric pain or if the patient suffers from coronary heart disease with angina pectoris I believe it preferable to discontinue smoking entirely In my experience patients find it easier to stop completely than gradually to reduce the number of cigars or cigarettes smoked daily I make a determined effort to persuade all cardiac patients to discontinue smoking

Coffee and Tea There is usually no objection to two or three cups of coffee daily In fact this may be desirable for patients with coronary heart disease But if this amount of coffee causes nervous irritability, sleeplessness, palpitation or indigestion, it should be avoided Sanka or weak tea may be substituted If strong tea is taken, the same limitations apply as for coffee

Bowels A satisfactory daily bowel movement is desirable Straining at stool must be avoided especially if the patient suffers from coronary heart disease There is danger of precipitating an acute coronary occlusion in such patients or of rupturing the heart wall if it is the site of a recent infarction The risk of pulmonary embolism due to straining has been mentioned Mineral oil (1 to 2 tablespoons) should be administered each night if the stool is hard A satisfactory bowel habit may be established if the patient tries to defecate each day at the same time and avoids other times For the first few days after a coronary occlusion or after the administration of opiates it is preferable to have no bowel movement at all unless this occurs easily and without catharsis Patients in bed usually require some assistance Mild laxatives such as milk of magnesia (1 to 2 oz), cascara sagrada (5 to 10 grains) or compound licorice powder (2 teaspoons) should be given nightly until a soft movement results Enemas should be given if necessary unless they weaken the patient unduly I have found a well given colon irrigation preferable to an enema and better tolerated by the patient

Cationic Exchange Resins[9, 231, 154, 348, [illegible], 59]

Adherence to very low sodium diets containing 500 mg or less daily is virtually impossible for some patients and very difficult for most especially if such dietary restriction must be continued for more than a few weeks After Dock[9] introduced the use of cationic exchange resins for the removal of sodium from the gastrointestinal contents, these resins gave promise of great therapeutic value in solving the problem of low sodium diets This promise has not yet been realized

Ion exchange resins are insoluble inert non absorbable ion-containing synthetic polymers of high molecular weight whose structure provides large surface areas permitting the selective exchange of its ions for other ions of similar charge Cationic resins are weakly acidic polyacrylic resins, usually containing either carboxylic or sulfonic groups, which remove from solution positive (basic) ions such as sodium, potassium and calcium in exchange for their own hydrogen, ammonium or other cations Sulfonic resins are effective at pH 3 to 10 and therefore actively exchange their ammonium or potassium ions for hydrogen ions in the stomach Subsequently the hydrogen ions are exchanged in the intestine for sodium potassium and calcium Ammonium ions released by the resins are absorbed and converted into urea by the liver Carboxylic resins are effective at pH 8 to 11 and are active in the alkaline intestine where their cations are exchanged for basic ions especially sodium

In vitro the cation resins show binding preference for ions with higher molecular weight and greater valence and therefore for calcium magnesium, potassium and sodium in this order But since the concentration of ions in solution is a determining factor, in the intestine the cationic resins bind predominantly sodium, which is highest in concentration and to a lesser extent potassium and calcium in that order In vivo, the binding power of the resins depends also on the sodium intake,[7, [illegible], 154, 381] 1 gm of resin binding about 1 to 1 5 mEq when the daily sodium intake is 2 gm or more, whereas 1 gm of resin may bind only 0 5 to 1 0 mEq of sodium when the daily sodium intake is only 200 mg to 1 gm The sodium binding of the cation resin is also dependent on the amount of sodium available for transport across the intestinal wall into the gut The sodium and other cations removed from the solution of intestinal contents may have originated exogenously in the diet or endogenously in the intestinal pancreatic or biliary secretions[106, 39, 348, 96]

The resins and the basic ions bound by them are not absorbed, but are excreted in the feces Clinical and experimental studies have shown that following the administration of cationic exhange resins the fecal excretion of sodium and potassium is increased and their urinary excretion diminished whereas the urinary excretion of chloride is enhanced[184, 27, [illegible], 104] A negative sodium balance may be achieved by marked increase in fecal sodium[39] If the administered cationic resin is of the hydrogen or ammonium series i e saturated with hydrogen or ammonium ions it releases these ions in the intestinal tract where

they combine with chloride the ultimate effect being similar to that of administered hydrochloric acid or ammonium chloride The action of the resin in depleting sodium in the intestinal contents is supplemented by the possible diuretic effect of an acidic chloride This may account in part for the observation that resins like ammonium chloride, may potentiate the diuretic effect of a mercurial [104, 39] The absorption of free chloride ions may not only increase the concentration of plasma chlorides but also reduces that of bicarbonate and induces acidosis[136, 154] the latter is usually mild and not responsible for clinical manifestations in the doses of resins usually prescribed The removal of potassium ions by resins may result in depletion of body potassium and hypokalemia[78, 154, 312] if this loss is not balanced by adequate dietary intake of potassium or potassium supplement Theoretically calcium may also be depleted, but balance studies show little increase in fecal calcium during resin administration and calcium depletion has not been a clinical problem

Preparations Dosage and Administration Three of the commercially available cationic resins are of the carboxylic type—Carbo Resin Resodec and Natrinil *Carbo Resin* contains 87 5 per cent cationic resin and 12 5 per cent anionic resin, the latter having been added to bind hydrogen ions in the stomach and thus neutralize the tendency of cationic resins to induce acidosis [97] The claim that addition of the anionic resin increases exchanging efficiency has been questioned The cationic resin itself in this preparation is two thirds saturated with hydrogen ions and one third with potassium The latter is designed to prevent potassium depletion and obviate the need for potassium supplements The recommended daily dose is 16 gm three times daily at mealtime This resin is available in bulk powder (1 pound bottles) or in 8 gm packets *Resodec* is saturated with ammonium and potassium ions in the ratio of 2 1 The recommended dose is 15 gm of powder (1 packet) three times daily at meals *Natrinil* is saturated four fifths with hydrogen and one fifth with potassium The recommended dose is 1 tablespoon or 1 packet (10 gm) four times daily i e at meals and on retiring A fourth cationic resin *Katonium* is a sulfonic type cation resin and is three quarters saturated with ammonium one quarter with potassium ions The dose is 15 gm three times daily at meals

The resins may be taken with water milk tomato juice, orange juice or other beverage including the colas or beer preferably chilled They may also be mixed with various foods such as cereals applesauce mashed potatoes Jello, ice cream Cookies and other preparations may be made with the resins according to recipes supplied by the manufacturers They have been administered continuously for prolonged periods without noticeable toxic effects [336, 343, 93, 345] but they may also be prescribed intermittently for periods of four or more days with intervals without resins [163]

Indications Clinical Value and Side Actions [77, 199, 81, 136, 154, 346] Resins are designed chiefly to reduce the amount of sodium absorbed when the dietary sodium restriction is inadequate to obtain the desired therapeutic effect Theoretically the same objective can be attained by minimizing the sodium intake to 200 mg or less as by use of the rice diet of Kempner In practice patients often cannot or will not follow such a regimen for the necessary prolonged period If the patient may be allowed a daily sodium intake of 1 2 gm (3 gm of sodium chloride) the diet can be made fairly tolerable the administration of resins at the same time serves to reduce actual sodium absorbed to the equivalent of that of a 200 to 400 mg sodium intake If 1 gm of the resin binds 1 mEq of sodium in the intestinal tract then 45 gm daily binds 45 mEq or about 1000 mg of sodium Thus only 200 mg of the 1200 mg of sodium ingested is absorbed

It is apparent however that the resins do not permit an unrestricted sodium intake when low sodium diets are necessary Nor do resins substitute for any other therapeutic measures indicated for the treatment of heart failure Mercurial diuretics may be required less frequently or not at all after the institution of resin therapy but this effect might be attained also if sodium intake were properly restricted It is questionable whether cationic resins should be used for the treatment of heart failure in patients who can be controlled on diets containing 1 2 gm of sodium or more daily

Essentially cation exchange resins are indicated in the treatment of heart failure when sodium intake must be limited to 200 mg daily and the patient refuses to follow this

regime or there is doubt as to his adherence to it It has been my experience many times that hospital patients supposedly on a 200 mg diet, excrete more sodium in their urine than appears possible if the diet were followed properly Following the administration of resins the urinary sodium falls to 7 mEq (200 mg) or less, and a more satisfactory clinical response is obtained than was previously possible There have been many reports of clinical improvement after institution of resin therapy when the response to all other conventional therapeutic agents had previously been unsatisfactory[198 105 863 199 27 96 259 25] The urine volume increased, the patient's weight fell and edema diminished or disappeared The need for mercurial diuretics was frequently minimized or abolished after institution of cation exchange resin Dyspnea and orthopnea have been relieved[118] Cationic exchange resins are indicated in all cases of intractable failure when there is no apparent cause for refractorness to treatment Several times I have noted a gratifying clinical improvement in patients with refractory heart failure after cationic resins were added to the therapeutic regimen Mercurials previously ineffective induced satisfactory diuresis and helped to restore compensation This is by no means the usual or even common effect of resins in refractory heart failure

The chief risk of cationic exchange resins is the development of metabolic acidosis with hyperchloremia, but this is rarely a significant danger except in the presence of renal insufficiency[348] The latter is generally regarded as a contraindication to cation resin therapy A second side action is the depletion of potassium in patients in whom the potassium bound by resin is not replaced by an adequate food intake because of anorexia or nausea Digitalis intoxication has been precipitated by potassium depletion due to resins[118] Resins intensify the potassium depletion that may result from concomitant diarrhea or the continued use of mercurial diuretics and ammonium chloride Potassium ions now included in the cation resins tend to reduce this risk Salt substitutes such as Diasal and Neocurtasal also help to supply potassium Potassium supplements may also be given In patients with hepatic dysfunction there may be some danger of ammonia intoxication if the ammonium type of resin is used Occasionally hypocalcemia may follow prolonged resin therapy,[154] but this may be prevented by giving 0 3 to 0 5 gm of calcium lactate or calcium gluconate orally three times daily Although the occasional complications of resin therapy should not be forgotten it is perhaps equally or more important to stress that cation resins have been administered for long periods of time without harm[335] Furthermore, such resin therapy has been safely administered to outpatients without complication even in the absence of strict chemical control[304]

From the practical point of view the chief objections to cationic resins include their usually unpleasant taste their bulk and their constipating effect Occasionally there are unpleasant digestive disturbances including anorexia nausea vomiting, epigastric burning abdominal cramps and diarrhea abdominal distention or fecal impaction Furthermore at the present time resins are relatively expensive for long term therapy Finally, patients generally refuse to continue the use of resins For all these reasons cation resin therapy after a brief flurry of endorsement has not taken hold in the management of heart failure Considering that the objective of resin therapy is to overcome the difficulty of maintaining extreme sodium restriction because of the impalatability of low sodium diets, the available resins have failed in that they are at least as impalatable or as difficult to take for many patients as the low sodium diets Nevertheless the therapeutic possibilities of the resins are such that it is to be hoped that they will continue to be improved with respect to the efficiency of their exchange capacity their consistency and palatability and not the least their high cost At the present time they may be useful as an adjunct when other measures for the treatment have failed or when the resins are tolerated better than the extremely low sodium diets

DIGITALIS AND RELATED DRUGS

Next to rest digitalis has been the most valuable agent in the treatment of congestive heart failure since Withering[255] in 1785 called attention to the beneficial effect of foxglove on dropsy In many cases of heart failure the combination of a brief period of bed rest and digitalization suffices to ameliorate or eliminate symptoms Many patients with limited cardiac reserve are enabled to conduct a

somewhat restricted but relatively normal life over a period of many years by the judicious restraint of physical exertion and the maintenance of digitalis therapy

THE ACTION OF DIGITALIS

The pharmacology of digitalis has been studied extensively (for details see the monographs of Cushny [74] Weese [328] Luten [201] and Moritt[247, 214]) but several of the actions of this drug are still obscure From the viewpoint of clinical application the following are most important

Improvement of Myocardial Function

The most important cardiac action of digitalis is a direct beneficial effect on myocardial contraction The digitalis glycosides enter the myocardial cells[140] where they yield active aglycones which in some unknown manner produce a more forceful systolic contraction of the heart There is experimental evidence suggesting that digitalis may favor the polymerization of actin and the shortening of actomyosin fibrils [278] Perhaps the latter is related to the effect of digitalis on myocardial potassium [62] membrane permeability to electrolytes and transmembrane potentials [3 3] which are concerned with the shortening of actomyosin (p 132) The studies of Clarke and Mosher[6] indicate that digitalis restores to normal values the diminished potassium and increased sodium concentration found in the heart muscle in congestive failure On the other hand infusions in dogs of acetyl strophanthin increased the potassium concentration in coronary sinus blood compared with arterial potassium concentration whereas the coronary sinus sodium concentration and the pH were lower This suggested that the drug caused potassium and hydrogen to leave and sodium to enter myocardial cells [174] Other studies with the aid of radioactive potassium (K^{42}) showed that digitalis reduced the exchangeable and tissue potassium content [15]

Studies of the effect of digitalis on myocardial metabolism indicate that the drug increases cardiac work in low output heart failure without a significant increase in coronary flow oxygen consumption or substrate extraction [21 3] Olson et al [257] observed that acetyl strophanthidin reduced glucose uptake without affecting the extraction of oxygen pyruvate or lactate Variable effects on contraction of the normal and failing heart were related to physical chemical properties of cardiac myosin

The over all effect of digitalis appears to be a more efficient utilization of phosphate bond energy by the actomyosin fibril [257 3] That digitalis promotes myocardial contraction has been repeatedly demonstrated experimentally in strips of heart muscle the isolated heart and the heart lung preparation [74 65] Schaefer [296] using the heart lung preparation demonstrated more forceful ventricular contraction and more complete emptying, the digitalized heart could expel its contents against a significantly higher arterial resistance than could the undigitalized heart More recently Cattell and Gold,[56] using the isolated papillary muscle of the cat and Kabat and Visscher [188] using the tortoise heart, similarly demonstrated striking increases in the force of systolic contraction and the work capacity of the heart muscle respectively following the administration of digitoxin ouabain or K strophanthoside Studies of the action potentials of single cardiac muscle fibers of the frog disclosed that digitalis and other cardiac glycosides shortened repolarization without affecting depolarization [365]

Digitalis not only increases the force of systolic contraction the capacity of the heart for work and the completeness of ventricular emptying but also enhances the efficiency of myocardial contraction For Gremels [150] using the heart lung preparation noted that following the administration of strophanthin the heart utilized less oxygen for a given amount of work Similar observations of Moe and Visscher[243] also indicated that digitalis bodies increase cardiac efficiency so that a greater percentage of energy expended is converted into external work Bing and associates[31 30] likewise reported that digitalization of patients with congestive heart failure resulted in an increase of the cardiac output without an alteration in coronary blood flow or oxygen consumption, hence there was an increase in mechanical efficiency In other words, digitalis increased the amount of mechanical work developed at a given oxygen expenditure—a reversal of the basic energy disturbance in myocardial failure [62 112] The effect of cardiac glycosides is apparently not on the production of energy but on the utilization of energy provided by the high-energy phosphate bonds [360] Studies in which human cardiac muscle was exposed

in vitro to radioactive (C^{14}) digitoxin suggested that digitoxin acts catalytically without itself being converted to carbon dioxide[50]

Because of these observations and others to be discussed below it appears probable that the major benefit of digitalis in heart failure is due primarily to its improvement in cardiac contraction and efficiency and only secondarily in certain cases to slowing of the heart rate Thus in cases with regular sinus rhythm, digitalis may lead to clinical improvement of heart failure without concomitant slowing of the heart rate or before such slowing occurs Furthermore although there is no direct conclusive evidence in humans such a myocardial action of digitalis has better experimental support and is more consonant with known observations than the suggested hypothesis of an extracardiac (peripheral vascular) action We have seen that the signs and symptoms of congestive heart failure and their localization are ultimately determined by the inability of a failing chamber to handle the venous return especially when this is increased during activity By augmenting the force of cardiac contraction and improving myocardial efficiency digitalis enables the venous return to be accepted and ejected, reduces the elevated venous pressure increases the cardiac output and restores compensation

Slowing of the Cardiac Rate

The rate of the heart is commonly accelerated in congestive heart failure, but this acceleration is especially pronounced and significant in those cases in which failure is associated with atrial fibrillation In the latter group especially digitalization rapidly effects a reduction in the ventricular rate to normal levels, concomitantly there is usually a striking amelioration in the clinical manifestations of heart failure Slowing of the heart by digitalis glycosides may be mediated by (a) vagal stimulation or (b) direct myocardial action on the atrioventricular node and bundle whereby their refractory period is prolonged[38] and atrioventricular conduction is depressed

Vagal Stimulation That digitalis produces slowing of the heart through vagal stimulation is indicated by observations both in animals and man, that such slowing is diminished or abolished by vagotomy or the administration of atropine[74] The vagal component is dominant with early therapeutic doses for Gold and his associates[149] showed that atropine increased the ventricular rate in atrial fibrillation after it had been slowed by digitalis But after full digitalization the rate could no longer be accelerated by atropine presumably because with larger doses slowing was mediated by extravagal means

The exact method by which digitalis induces vagal slowing of the heart is uncertain Heymans and his co-workers,[178] in cross circulation experiments, slowed the heart rate of dogs by perfusing the carotid sinus with digitalis Similar perfusion of the vagus center produced no slowing if the center was isolated from the afferent sinus nerves These experiments suggested that digitalis slowing was effected by action of the drug on the perceptors of the carotid sinus with a consequent reflex increase in vagal tone, and a diminution of the rate of impulse formation in the sinoatrial node

However, there is more evidence that this reflex vagal effect at least in congestive heart failure is not due to direct action of digitalis on the sinus receptors, but to afferent stimuli initiated when the failing heart muscle is restored to compensation by direct myocardial effects of digitalis In persons with normal hearts digitalis causes slight or no slowing except with toxic doses Digitalis reduces the cardiac rate in tachycardias only when the tachycardia is due to heart failure In patients with atrial fibrillation digitalis induces more striking slowing of the heart when there is associated heart failure than in cases of atrial fibrillation without heart failure All these observations seem to support the concept that digitalis in therapeutic doses exerts its slowing effect essentially in the presence of failure and that the reduction in cardiac rate is secondary (by way of vagal reflexes) to the digitalis induced improvement in myocardial function[2 1]

That tachycardia is a compensatory reaction to cardiac failure has been discussed Presumably the tachycardia is initiated by an elevation of venous pressure with a consequent Bainbridge reflex Elimination of this tachycardia requires abolition of the myocardial failure which induced the increase in heart rate By causing a more forceful cardiac contraction and more complete emptying digitalis relieves the heart failure, reduces the venous pressure and abolishes the reflex responsible for the compensatory tachycardia

Depression of Atrioventricular Conduction

Digitalis impairs the conduction of impulses from the atrium to the ventricle partly by vagal stimulation but also and predominantly through the direct action on the junctional conduction tissues. This occurs both in healthy and decompensated hearts and is disclosed electrocardiographically by prolongation of the P-R interval and with more toxic doses by more severe degrees of atrioventricular heart block. Lewis and his co-workers[214] demonstrated a digitalis-induced inhibition of atrioventricular conduction even when vagal depression was excluded by atropine in dogs in which the atria were stimulated to produce a rapid atrial rate as in fibrillation. According to Mendez and Mendez[33] the diminution in atrioventricular conduction to the point of atrioventricular block is due to an increase in the refractory period of the atrioventricular propagating tissue.

According to Mackenzie[23] and to Lewis[38] depression of atrioventricular conduction by digitalis accounts for its usefulness in cases of atrial fibrillation with rapid ventricular rate in which the drug's most striking benefits are clearly demonstrable. When the atria fibrillate they may discharge 400 or more impulses per minute to which the harried ventricles may respond with 100 to 160 contractions per minute. But these ventricular contractions are less efficient than normal because (a) the diastolic recovery period is diminished by the tachycardia and (b) the atrial impulses arrive so rapidly and irregularly that many ventricular contractions occur too soon after the previous one to permit adequate filling or expulsion of blood. Therefore many of the ventricular contractions are too weak to open the aortic valve or produce a palpable radial pulse (pulse deficit).

According to the Mackenzie[5] concept digitalis by impairing atrioventricular conduction diminishes the frequency of impulses bombarding the ventricles and thereby slows the ventricular rate. Consequently more effective systolic contraction and emptying are possible, the pulse deficit is eliminated and compensation restored. According to Luten and Jefreys the digitalis effect on atrioventricular conduction is of secondary importance in accounting for myocardial improvement in cases of atrial fibrillation and heart failure. As stated above clinical improvement is attributed to direct action of digitalis on the myocardium with stronger cardiac contraction. The ventricular slowing is then due (a) partly to vagal reflexes as myocardial function improves and (b) to increase in the refractory period of the ventricular myocardium due to its stronger contraction thereby rendering the heart muscle unresponsive to most of the atrial impulses. According to this explanation increased myocardial refractoriness due to more forceful contraction is more important than impaired atrioventricular conduction in explaining the digitalis effect in cases of atrial fibrillation with heart failure. On the other hand recent studies by Mendez and Mendez[35] indicate that while digitalis increases the refractory period of the atrioventricular conduction system, it shortens the refractory period of ventricular muscle and that the latter accounts for the occurrence of ventricular premature beats and the susceptibility to digitalis ventricular fibrillation. However these effects may appear only with relatively large doses.

Peripheral Action of Digitalis

The possibility that the beneficial effect of digitalis in congestive heart failure is due essentially to a peripheral action[10] whereby the venous return is diminished by venoconstriction is discussed below under the heading Cardiac Output and Venous Return.

Digitalis and Cardiac Size

There is uniform agreement that in the heart-lung preparation in normal animals, in normal persons and in patients with congestive heart failure digitalis reduces the size of the heart.[65, 316, 44] Cardiac failure is associated with an enlarged heart which as shown by Starling and Visscher[314] is inefficient because it consumes relatively more oxygen than the normal heart for the performance of the same amount of useful work. By diminishing the size of the dilated decompensated heart digitalis increases its fitness or functional capacity so that it carries out its work with a lesser volume, a lesser oxygen consumption and therefore with greater efficiency.

On the other hand one must not mistake cause and effect. The development of cardiac enlargement in congestive heart failure is a consequence of an increasing residual of blood with increased lengthening and hypertrophy of the myocardial fibers. This may serve as a compensatory mechanism by which the fa

tigued and damaged heart attempts to maintain an adequate output. Conversely, reduction in size of the enlarged heart by digitalis may not be a direct effect of digitalis but rather a reversal of the process of dilatation as the digitalis promotes the strength and efficiency of myocardial contraction. Consequently there is less residual of blood, less stretch of myocardial fibers and less "compensatory" enlargement than before digitalization. The experiments of Cattell and Gold[58] indicate that digitalis acts directly on the heart muscle to increase the tension which it can develop during systolic contraction without a primary change in the diastolic length of the muscle. In addition to the direct benefit of digitalis for the heart muscle, the secondary reduction in heart size is itself advantageous because of the lesser oxygen requirement and the greater efficiency of cardiac contraction.

Digitalis and Circulatory Dynamics

The clinical benefit of digitalis in heart failure has been shown to be based primarily on its direct improvement of myocardial contraction and efficiency and in part or secondarily on slowing of the cardiac rate. In addition digitalis tends to restore to normal the various aberrations in circulatory dynamics which develop in the course of heart failure. These effects, like the reduction in cardiac size, are probably not direct consequences of digitalis activity but secondary to strengthening of cardiac contraction and enhanced cardiac emptying.

Cardiac Output and Venous Return. In the heart lung preparation digitalis may produce a temporary increase in cardiac output after the heart dilates. But in normal dogs, in dogs with compensated valvular lesions and in normal men, digitalis reduces the cardiac output.[65, 92, 316]

In cases of heart failure Stewart and his associates[316] and others[1, 9, 101] observed an almost constant increase in cardiac output following digitalization. McMichael and Sharpey Schafer,[235] using the method of intracardiac catheterization, observed striking and *uniform* augmentation of cardiac output following the administration of digitalis to patients with congestive heart failure. Bloomfield et al.,[33] using the same technique, observed a uniform increase in cardiac output (due to increase in stroke volume) following the intracardiac administration of 0.25 to 0.75 mg. of ouabain.

To account for the diminished output of normal hearts following digitalization, Dock and Tainter[92] concluded that digitalis caused a diminution in the venous return, probably by a constriction of the hepatic veins. This was based on the observations in dogs that digitalis caused not only a diminution in cardiac output but also a simultaneous reduction in venous pressure and an increase in the volume of the liver and of the portal venous pressure. However, an hepatic venoconstrictor (throttle) mechanism such as occurs in the dog could not be demonstrated in humans.[9]

McMichael and Sharpey Schafer[235] likewise concluded that digitalis exerted a peripheral venoconstrictor action in congestive heart failure, for the *increase* in cardiac output and fall in venous pressure mirrored closely similar changes produced by venesection or by the application of tourniquets. They concluded that digitalis, by causing venoconstriction, diminished the venous return and thus enabled the overloaded heart to contract more efficiently and augment its cardiac output. But with respect to congestive heart failure *the digitalis induced enhancement in cardiac* output and fall in venous pressure can be more satisfactorily explained by the direct myocardial action of digitalis with consequent improvement in cardiac contraction and emptying. With respect to the reported diminution in cardiac output following digitalization of normal hearts, it is probable that this is related to a reduction in blood volume and venous return, but it is unnecessary to assume a digitalis action on the peripheral veins. Here too a direct myocardial effect may be primary, with subsequent increase in renal excretion of sodium and water, diminution in blood volume and reduction in the venous return.

Circulating Blood Volume. Digitalis diminishes the circulating blood volume both in normal individuals[26] and in subjects with congestive heart failure.[101] We have seen that the increased blood volume in congestive heart failure results from renal retention of sodium and water which may serve as a compensatory mechanism to restore a deficient cardiac output. Digitalization, by improving cardiac contraction and cardiac output, reverses this series of events and diminishes the blood volume.

Venous Pressure. The venous pressure is

diminished after the administration of digitalis to patients with heart failure[101] This is best explained by improvement in cardiac contraction and emptying whereby the venous return is more effectively handled and damming of blood in the inflow veins to the failing chamber is eliminated In the observations of Bloomfield et al[32] an improvement in cardiac output preceded any fall in venous pressure In cases of isolated left ventricular failure Ferrer et al[1 0] observed that the administration of digoxin was followed by an augmented cardiac output and a sharply reduced pulmonary artery pressure but there was no effect on the central venous pressure

Circulation Time The circulation time of normal patients is not affected by digitalis But in patients with congestive heart failure the prolonged circulation time is diminished[316, 203]

Intracardiac and Pulmonary Blood Pressure In patients with right ventricular failure the right atrial pressure falls as does the venous pressure and the elevated right ventricular pressure diminishes[35, 166, 101] The pulmonary blood pressure when elevated by left-sided heart failure decreases after digitalization[204, 1 0] In cases of chronic pulmonary disease with right-sided heart failure the cardiac output increases and the right ventricular diastolic pressure falls after digitalis, but the pulmonary arterial blood pressure rises[1 0]

Digitalis and Electrolyte Excretion and Renal Function

Digitalis produces a prompt increase in the excretion of sodium and water in patients with congestive heart failure[117, 8] There is an enhanced renal plasma flow and glomerular filtration and a diminution in the filtration fraction and renal venous pressure However the improvement in excretion of sodium and water is not distinctly related to changes in glomerular filtration

INDICATIONS FOR DIGITALIS THERAPY

1 Congestive heart failure with regular sinus rhythm or with atrial fibrillation This is the primary indication for digitalis

2 Atrial fibrillation especially when the ventricular rate is rapid or congestive heart failure is present

3 Atrial flutter

4 Prevention and treatment of recurrent episodes of paroxysmal atrial tachycardia

Congestive Heart Failure

Digitalis is indicated primarily and most frequently in the treatment of congestive heart failure due to myocardial strain or impairment regardless of etiology Digitalis is indicated whether heart failure is mild or severe whether the rhythm is regular or irregular, whether the rate is rapid or not and whether or not heart block (unrelated to digitalis) is present In cases of heart failure in which some known remediable factor is the precipitating cause e g infection anemia hyperthyroidism correction of the precipitating factor may be more important but the administration of digitalis is also indicated at least until heart failure is abolished

Heart Failure with Atrial Fibrillation or Flutter The most dramatic therapeutic effects of digitalis are observed in cases of heart failure and atrial fibrillation especially when the ventricular rate is so rapid as to impair ventricular filling or cut into the recovery phase of diastole With digitalization ventricular rates of 120 to 150 may be rapidly reduced to 60 to 80 per minute and a pulse deficit is eliminated Concomitantly the manifestations of congestive heart failure such as dyspnea or venous engorgement are ameliorated or annulled If palpitation precordial distress or weakness is due to the rapid irregular ventricular rate these symptoms are relieved as the rate is slowed by digitalis

Digitalis should be administered to patients with congestive heart failure and atrial fibrillation even though the ventricular rate is not rapid The essential purpose of digitalization in cases of congestive heart failure is the improvement of the function of the myocardium and not the modification of the ventricular rate

Digitalis often exerts striking therapeutic effects in patients with heart failure and atrial flutter Frequently the digitalis not only slows the heart but converts the atrial flutter into atrial fibrillation Although stoppage of digitalis may be followed by restoration of regular rhythm this is unlikely to occur and the digitalis should not be discontinued for this purpose in cases of organic heart disease with enlarged hearts and chronic heart failure

Heart Failure with Sinus Rhythm The value of digitalis is usually less striking in cases of heart failure with regular rhythm than in those with atrial fibrillation, nevertheless its benefit is sufficiently clear[221, 171, 125, 120, 166]

Gavey and Parkinson[128] found digitalis efficacious in more than half of 47 cases of congestive heart failure with sinus rhythm and concluded that digitalis was indicated in the treatment of congestive heart failure irrespective of the rhythm. In many of the observations made in patients with heart failure and regular rhythm, digitalis reduced the cardiac rate without notable clinical benefit, in others clinical improvement occurred without a change in the heart rate, but in general clinical benefit and slowing of the heart occurred concomitantly. Flaxman[148] reported that digitalis was more effective in cases of heart failure with normal rate than in those with sinus tachycardia. He concluded that the beneficial action of digitalis was on the myocardium and not on the ventricular rate.

In a clinical study by Wood[361] digitalis effected demonstrable improvement in 18 of 20 patients with congestive heart failure and normal rhythm. Repeated determinations of the venous pressure were utilized to evaluate progress in his cases of right sided heart failure, and the arm to tongue circulation time in his cases of left heart failure. He likewise observed that a diminution in the cardiac rate was usually associated with improvement from digitalis therapy but in 2 cases there was no such alteration in rate despite distinct benefit. It is clear from these and other studies that digitalis produces clinical improvement in congestive heart failure by direct beneficial action on the heart muscle which is independent of its effect on cardiac rhythm or slowing of the cardiac rate.

The beneficial effect of digitalis is not limited to cases of right sided heart failure with venous congestion, hepatic enlargement and peripheral edema. Some of the most striking results are obtained in patients with isolated left sided failure[15, 16]. Thus dyspnea on exertion or at rest, orthopnea, cardiac asthma, nocturnal cough when due to the pulmonary congestion of heart failure are all indications for the administration of digitalis. In a series of cases of pure left sided heart failure Harrison, Calhoun and Furley[165] found that digitalis relieved the dyspnea and attacks of cardiac asthma and concomitantly increased the vital capacity and the speed of circulation.

Atrial Fibrillation (See also p 364)

Digitalis is most clearly indicated and is particularly beneficial in those cases of atrial fibrillation and rapid ventricular rate which are associated with congestive heart failure. Usually these are cases of coronary and hypertensive heart disease or of rheumatic heart disease with mitral stenosis. It is still a moot question whether the striking efficacy of digitalis in these cases is due exclusively or essentially to direct improvement in the efficiency of the failing myocardium[2, 203] or in large measure to indirect improvement mediated by impairment of atrioventricular conduction and consequent ventricular slowing. Digitalis does not abolish atrial fibrillation, in fact its direct or reflex effect on the vagus nerve by reducing the refractory period of atrial muscle, or its increase of atrial myocardial excitability, tends to perpetuate fibrillation (p 364).

When digitalis reduces the ventricular rate to between 60 and 80 per minute in cases of atrial fibrillation and heart failure it must be continued in the dosage necessary to maintain the desired ventricular rate and other clinical effects. However atrial fibrillation with normal or slow ventricular rate is sometimes encountered in the absence of heart failure. There are usually no symptoms and there is no indication for digitalis.

When atrial fibrillation with rapid ventricular rate is due to hyperthyroidism alone digitalis is not indicated unless there is evidence of heart failure. Neither is it indicated in the cases of atrial fibrillation due to a variety of less common causes of toxic, traumatic, infectious, neoplastic or other origin.

Atrial Flutter (See also p 357)

Digitalis is indicated in cases of congestive heart failure associated with atrial flutter, and in cases of atrial flutter with organic heart disease and pronounced enlargement of the atrium or ventricles. Digitalis is also indicated in cases of atrial flutter without heart failure or cardiac enlargement but its effectiveness is quite variable.

Digitalis may abolish atrial flutter but tends to convert it into atrial fibrillation by increasing the excitability of the atrial musculature. Large doses of digitalis are required and mild atrioventricular block may be produced. In most cases without serious organic heart disease, discontinuance of digitalis when atrial fibrillation has developed is followed by a reversion to regular sinus rhythm. But regular sinus rhythm may appear without the intermediary of atrial fibrillation and

without discontinuation of the digitalis If atrial flutter recurs repeatedly or if atrial fibrillation persists digitalis therapy may have to be continued in order to maintain optimal slowing of the ventricular rate In 100 cases of atrial flutter treated by digitalis Luckey [19] reported that normal sinus rhythm was established in 46 while digitalis was being continued in 32 the flutter was converted into atrial fibrillation with well controlled ventricular rate and in the remaining 22 atrial flutter persisted at a lower ventricular rate owing to a higher degree of block

Paroxysmal Tachycardia

The initial therapeutic measures recommended for the control of paroxysmal atrial tachycardia are discussed elsewhere (p 318) If carotid sinus pressure and induction of other vagal reflexes have failed to control an attack of paroxysmal tachycardia and especially if heart failure ensues digitalis may be given orally But many cardiologists employ a parenteral digitalis preparation as the initial form of therapy Preparations for intravenous injection (ouabain Cedilanid etc p 257) should be used if rapid action is important [107] Digitalis glycosides have also been recommended for prophylactic use in the prevention of recurrent paroxysmal arrhythmias

FACTORS MODIFYING THE INDICATIONS FOR DIGITALIS

Digitalis has been found to be more effective in certain cases of congestive heart failure or atrial fibrillation than in others Such apparent discrepancies will be clear if the actions of digitalis are kept in mind For digitalis can be beneficial only if the symptoms are due either to impaired myocardial *function which can still be helped by the drug* or to a rapid ventricular rate secondary to atrial fibrillation which can be slowed by impairing atrioventricular conduction Thus digitalis is ineffective in cases of cardiac failure due to *mechanical impediments* such as constrictive pericarditis extreme mitral stenosis or atrial thrombi occluding the mitral orifice It is also ineffective when myocardial damage is too severe or extensive to permit the heart muscle to respond to the medicament Digitalis is often of little help when the causative factor of heart failure is still active e g active rheumatic fever diphtheria Graves disease myxedema avitaminosis severe anemia or arteriovenous aneurysm In such cases medical or surgical elimination of the cause should be the essential element in therapy and digitalis only an accessory There is evidence that in various forms of high-output heart failure such as that due to hyperthyroidism beriberi and the like there is a metabolic impairment in energy formation in the heart muscle whereas in the more common low output heart failure the basic disturbance is in energy utilization [65] Since digitalis and related cardiac glycosides appear to improve energy utilization by the myocardium these drugs are of little or no value in forms of heart failure due exclusively or almost entirely to a defect in energy formation

CONTRAINDICATIONS AND NON INDICATIONS FOR DIGITALIS THERAPY

Arrhythmias and Tachycardias

Digitalis is not indicated for the treatment of tachycardias due to infections or fevers to hyperthyroidism drugs or neurocirculatory asthenia unless congestive heart failure is present Digitalis has been said to be contraindicated in the presence of premature contractions because of the danger of producing ectopic beats but the latter result only from toxic doses of the drug If cardiac failure appears the coexistence of premature beats does not contraindicate the use of digitalis Sometimes digitalis appears to dispel protracted premature beats with or without associated heart failure Similarly digitalis may occasionally terminate a prolonged paroxysmal tachycardia Digitalis is not indicated or contraindicated in the presence of ventricular tachycardia However if the patient also has congestive heart failure and is digitalized there is no need to discontinue digitalis unless there is a suspicion that the digitalis is responsible for the tachycardia Similarly digitalis may be given if the heart failure is the consequence of protracted ventricular tachycardia not due to digitalis [11] Other drugs should be given simultaneously to control the tachycardia (p 371)

Conduction Disturbances

Digitalis has frequently been said to be contraindicated in cases of *partial heart block* because of the danger of further impairment of atrioventricular conduction and the consequent *development* of complete heart block On the other hand Eggleston[29] obtained satisfactory results with the use of digitalis the block sometimes disappearing

when heart failure was relieved In a study of 19 patients with various grades of heart block, most of whom were suffering from congestive heart failure Blumgart and Altschule[85] administered digitalis in sufficient dosage to produce a therapeutic effect without observing any increase in the degree of block In some cases the P-R interval was shortened as the patient improved under digitalis therapy

In patients with *complete heart block*, digitalis is indicated only if there is congestive heart failure In the latter cases good therapeutic effects may be obtained with improved myocardial function The degree of block cannot be further increased However because of its vagal action digitalis may be undesirable in patients with frequent Adams-Stokes attacks or carotid sinus hypersensitivity[254]

Digitalis is not indicated in cases of sinus arrhythmia, sinoatrial block nodal rhythm or ventricular escape except when associated with heart failure These arrhythmias are often due to digitalis toxicity

Coronary Heart Disease

Coronary heart disease with angina pectoris or recent coronary occlusion is in itself neither an indication nor a contraindication to the use of digitalis Reports of the development or exacerbation of cardiac pain following the administration of digitalis[129] have led to hesitancy in using the drug in patients with angina pectoris for fear of causing vasoconstriction of the coronary arteries Freedberg and his associates[139] called attention to the similarity between the electrocardiographic changes associated with angina pectoris and those induced by digitalis But while the ST depressions observed with the former are related to subendocardial ischemia, the ST depressions caused by digitalis are due to another mechanism (p 270) There is no definite evidence that therapeutic doses of digitalis have a significant direct effect on coronary blood flow[113] Furthermore Gold Otto and associates[150] in a study of 120 patients with angina pectoris who were treated by alternating courses of digitalis and a placebo concluded that digitalis medication does not produce cardiac pain The beneficial effect of digitalis on the heart rate and efficiency of cardiac contraction in cases of heart failure should serve indirectly to promote the coronary blood flow, for the coronary flow is augmented in proportion to the work of the heart when the rate is slowed and the stroke volume increased (p 130) Digitalis should be given to patients with heart failure even if they suffer from angina pectoris

Similarly digitalis is not contraindicated if congestive failure develops in a patient with an acute coronary occlusion (coronary thrombosis) (p 579)

Shock and Infection

Digitalis is contraindicated in cases of central or peripheral circulatory failure associated with shock Digitalis further reduces the low blood volume and the insufficient output of the heart Postoperative shock is an example of a condition in which digitalis continues to be employed without benefit and probably with harm to the patient Digitalis is not indicated in cases of circulatory shock accompanying infections such as pneumonia or diphtheria A controlled study of a series of 834 cases of lobar pneumonia, in which alternate patients were given digitalis revealed a slightly higher mortality in the digitalized group[366] In cases of rheumatic fever digitalis is not indicated but when congestive heart failure appears the drug should be administered As a rule the benefits are not striking if there is rheumatic activity and large doses of the drug are required When shock and acute ventricular failure occur simultaneously in cases of acute myocardial infarction digitalis may be given and is sometimes of dramatic benefit if the left ventricular failure is a dominating element in the clinical picture

Surgical Procedures

Digitalis has been used extensively and unjustifiably in many patients who undergo surgical procedures There is no proof of its value preoperatively unless congestive failure is already present or unless the patient is subject to frequent attacks of paroxysmal atrial fibrillation, one of which may be precipitated by the operation Following operation, digitalis is not indicated either for cardiovascular collapse (shock) tachycardia or premature beats, all of which occur frequently

Hypertension and Nephritis

Hypertension is no contraindication to the use of digitalis in the treatment of heart failure An elevated blood pressure associated with heart failure (*Stauungshochdruck*) may fall when digitalis relieves the failure On the other hand cardiac failure may be accompanied by a fall in blood pressure which in

creases again when the heart recovers after digitalis therapy Digitalis is also well tolerated in patients with nephritis associated with congestive heart failure

Concomitant Drugs

Digitalis administration has been said to be dangerous or contraindicated in patients receiving calcium ephedrine or quinidine All of these drugs must be given with great care especially when administered intravenously to patients with heart failure But that their possible danger is due to synergism with digitalis is unproven neither is digitalis contraindicated when patients are receiving these drugs or vice versa

Compensated Heart Disease

I do not give digitalis prophylactically to patients with compensated heart disease unless digitalis was previously employed during heart failure

Toxic Symptoms

The chief contraindication to the administration of digitalis is the presence of symptoms due to overdosage of this drug (see p 264)

PREPARATIONS AND DOSAGE OF DIGITALIS

Powdered Whole Leaf

Until recently the powdered whole leaf of digitalis was the preparation recommended by the Digitalis Committee of the American Heart Association and it is probably still used widely It is a galenic preparation obtained from the dried leaves of Digitalis purpurea in the second year of growth of the plant and administered in the form of tablets capsules or tincture and rarely in suppositories or infusions The tablets pills and capsules usually contain 0 1 gm (1½ grains or 1 U S P unit) each and possess the advantage of accurate dosage and convenience of administration The tincture of digitalis which is a 10 per cent alcoholic solution of the leaf has also been used extensively and will not deteriorate for a long time if kept in a properly stoppered bottle Deterioration due to actinic rays is minimized by keeping the tincture in a brown bottle and by decolorizing with animal charcoal and adding aniline red [119] An accurate minim dropper is essential for measuring the dose

Dosage of Powdered Leaf of Digitalis The digitalizing dose is about 1 2 to 2 0 gm of U S P digitalis leaf or 12 to 20 cc of the tincture The subsequent maintenance dose is 0 1 to 0 15 gm or 1 0 to 1 5 cc of the tincture Details of digitalization and maintenance are discussed below

Absorption of digitalis leaf is relatively poor i e only about one fifth of the administered dose About 0 1 to 0 2 gm is excreted daily after full digitalization

Digilanid

Effective digitalis glycosides can be obtained from the leaf of Digitalis lanata as well as the more commonly employed Digitalis purpurea The essential ingredients of Digitalis lanata and their approximate proportions are lanatoside A—46 per cent lanatoside B—17 per cent lanatoside C—37 per cent Digilanid is a preparation of constant composition in which the impurities of the crude leaf have been removed and the pure active lanatosides A B and C have been combined in the above percentages It is provided in 0 33 mg tablets = 1 cat unit

Dosage of Digilanid The digitalizing oral dose ranges between 3 0 and 8 0 mg with daily doses of 0 33 mg for maintenance The intravenous digitalizing dose is 3 0 mg

Digitoxin and Other Pure Digitalis Glycosides

Digitoxin is a relatively pure crystalline digitalis glycoside isolated from digitalis leaf in a more purified form than the digitaline crystallisée of Nativelle Digitoxin gitoxin and gitalin are the glycosides obtainable from Digitalis purpurea leaf Digitoxin can also be obtained by hydrolysis of lanatoside A and gitoxin from lanatoside B of the Digitalis lanata leaf Lanatoside C yields digoxin which is unobtainable from Digitalis purpurea The chief advantage of digitoxin and other digitalis glycosides is their uniform and constant potency which makes it possible to administer them by weight and eventually dispense with biological assay The toxic symptoms of overdosage with cardiac glycosides are identical with toxic symptoms caused by the whole leaf preparations

Digitoxin is completely absorbed from the intestinal tract as indicated by the fact that the digitalizing dose is identical whether the drug is given orally or intravenously [111] There is no nausea or vomiting due to local gastric irritation but central nausea occurs with excessive dosage of digitoxin as with other digitalis preparations [112] The absence of gastrointestinal disturbance is attributed to freedom of the drug from irritating impurities rapid and complete absorption and the

minute dosage required for therapeutic effectiveness. Compared to other glycosides digitoxin has a relatively long latent period. Its activity begins one hour after intravenous administration and its maximum effect requires four hours or longer. The chief disadvantage is its long period of dissipation, two to three weeks being required for elimination. Studies on radioactive digitoxin administered to patients with heart failure indicate that unchanged digitoxin is excreted in the urine for as long as 40 days after the administration of a single dose.[57] Therefore when toxic symptoms appear they are relatively persistent. On the other hand, the slow elimination of digitoxin may also be considered an advantage because digitalization can be readily maintained for a long time.

Acetyldigitoxin is closely related chemically to digitoxin except for an acetyl group in its structure. It was reported to have the advantages of digitoxin but with less toxicity and somewhat faster dissipation. The digitalizing dose is 1.6 to 2.0 mg. and the maintenance dose 0.15 mg. (0.1-0.2 mg.)[21, 78]

Dosage of Digitoxin. The digitalizing dose was said to be 1.2 mg. when given in a single dose[144] but some patients require 2.0-2.5 mg.[33, 87, 117] I have repeatedly observed toxic symptoms with the lesser dose (1.2 mg.) but as a rule this dose is inadequate for digitalization. The average daily maintenance dose is stated to be 0.2 mg. but often 0.1 or 0.15 mg. or as little as 0.05 mg. suffice. It is apparent that digitoxin is approximately 1000 times as powerful as digitalis leaf, i.e., 0.1 mg. digitoxin = 0.1 gm. digitalis leaf.

Dogmatic oversimplification of dosage directions has lent unusual appeal to this preparation and has resulted on the one hand in inadequate digitalization in some patients, and on the other in toxic manifestations in other patients who require less than the recommended dose of 1.2 mg. Thus De Graff and his associates[87] found that only 17 per cent of patients were satisfactorily digitalized with 1.2 mg. of digitoxin, and that 1.7 mg. was the average single therapeutic dose. At the same time I have observed a pronounced increase in the occurrence of digitalis toxicity since digitoxin has been administered in the prescribed fixed dosage of 1.2 mg. for digitalization and 0.2 mg. daily for maintenance. In general, the recommended digitalizing dose of 1.2 mg. of digitoxin is inadequate, and the recommended maintenance dose of 0.2 mg. daily is excessive and eventually toxic. This high maintenance dose is responsible for the high incidence of toxic manifestations observed since the glycoside was recommended. Flaxman[116] recently reported 30 cases of digitoxin poisoning in patients who had taken the recommended doses of the drug. The earliest and commonest symptoms were disturbances in conduction including prolongation of the P-R interval and a-v dissociation. Master[9] described 9 cases of digitoxin poisoning with gastrointestinal and psychic symptoms, arrhythmias, atrial, nodal and ventricular tachycardia, partial and complete heart block and electrical alternans.

Digoxin

This is a pure crystalline glycoside derived from the leaves of Digitalis lanata and is closely related to lanatoside C. It is the one glycoside obtained from Digitalis lanata not obtainable from Digitalis purpurea. Like digitoxin it is a pure substance of definite and constant composition which can be prescribed in terms of weight of the pure drug. Its pharmacologic effects are identical with those of the whole leaf of digitalis or any of its glycosides.[78] A new related oral preparation, *acetyldigoxin*, obtained from lanatoside C, has recently been studied.[108, 215] The digitalizing dose is usually 2.0 to 5.0 mg., the maintenance dose 0.4 to 0.7 mg. daily.

According to De Graff,[85] digoxin, like digitoxin, is thoroughly and quickly absorbed from the gastrointestinal tract, but there is some uncertainty regarding this point. Digoxin is rapidly eliminated from the body which bears the advantage of less likely and briefer toxicity but also the disadvantage of greater difficulty in maintaining continuous digitalization. Elimination of a full digitalizing dose is complete in about 48 hours if no further digitalis has been given.[9] Therefore if there is uncertainty as to recent digitalis intake digoxin may be safer to administer than other digitalis preparations.

Dosage of Digoxin. The average digitalizing dose of digoxin given within 24 hours is about 3.75 mg. with a range of 2.0 to 5.0 mg.[85, 115] A dose of 1.5 mg. of digoxin usually produces a digitalizing effect in one or two hours and becomes maximal in six to eight hours. Additional doses of 0.25 mg. or 0.5 mg. may be given at [illegible] hour intervals to full digitalization. The daily maintenance dose

is 0.25 to 0.5 mg, occasionally only 0.125 mg, compared to 0.1 to 0.2 mg for digitoxin. Because of low solubility in water, digoxin is prepared for intravenous use in alcoholic solution, which must be diluted with saline before use. The intravenous dose is 0.75 to 1.0 mg, which produces an effect in 10 minutes and has maximal activity in one to two hours. In the rare instances in which digitalis must be given intravenously, other digitalis preparations are preferred (p. 262).

Gitalin

This is an amorphous, highly purified, water-soluble glycoside obtained from Digitalis purpurea and is the only glycoside obtained from Digitalis purpurea not also obtainable from Digitalis lanata. Gitalin, marketed as Gitaligin, is of uniform potency, is absorbed more rapidly and completely than digitalis leaf and is about 200 times as potent weight for weight. Its rate of elimination or dissipation (3 to 4 days) is equal to or slightly slower than that of digoxin, but more rapid than that of digitoxin. Its pharmacologic effects are virtually identical with those of the other digitalis glycosides and digitalis leaf. These similarities apply also to its toxic effects with excessive dosage.

Although gitalin has been available for a long time and its effectiveness reported for many years,[8, 2, 311] it has only recently attained a wide and enthusiastic following because of the claim that it has the widest range of safety (between its therapeutic and toxic doses) of any of the digitalis preparations. Thus Batterman and associates found that, whereas the ratio of the therapeutic to the toxic dose for digitoxin, digoxin and digitalis leaf, respectively, varied from 58 to 66 per cent,[8] the therapeutic to toxic dose ratio was only 37 per cent for gitalin.[14, 245] Furthermore, it has been claimed that gitalin may be effective when there is no further response to other digitalis preparations or when these had to be discontinued before therapeutic effectiveness because of toxic manifestations. If these claimed advantages are substantiated, gitalin would appear to be the most desirable digitalis preparation for oral use. That gitalin may be tolerated and prove effective when other digitalis preparations do not has been reported by other observers,[172, 85] but Hejmancik and Herrmann[173] could not confirm the wide therapeutic ratio reported by Batterman et al.[14] In general I am skeptical of claims of less toxicity of one digitalis preparation compared to another when comparative dosage and therapeutic effects are considered. There are obvious difficulties in quantitative titration of digitalis preparations in dealing with human patients and especially in trying to distinguish therapeutic effects, toxic effects and manifestations of heart failure itself.

Dosage of Gitalin (Gitaligin). The average digitalizing dose has been variously found to be 5.0 to 6.5 mg,[14, 164] but the range is between 3.0 and 10.5 mg. The maintenance dose is most commonly 0.25 to 0.5 mg and occasionally 0.75 mg to 1.0 mg daily. Gitalin may be administered intravenously, its digitalizing dose being identical with that when given orally,[163] namely, 2.5 mg to 3 mg initially and repeated in 24 hours. Maintenance is by two injections of 2.5 mg weekly. For rapid oral digitalization 5 tablets (2.5 mg) of Gitaligin are administered at once, then 1½ tablets (0.75 mg) of Gitaligin are given every six hours. Digitalization is thus effected in 24 to 36 hours. For slow digitalization 3 tablets (1.5 mg) are administered daily for four to six days.

Lanatoside C

Lanatoside C, marketed under the trade name of Cedilanid, is an initial crystalline glycoside related to digoxin and likewise derived from Digitalis lanata leaf. Compared with the other two commonly employed glycosides already discussed, lanatoside C has the shortest latent period and the most rapid elimination. The speed of elimination makes it less satisfactory than digitoxin for oral use because it is difficult to maintain digitalization and relatively high initial dosage is required. On the other hand, the brief latent period makes lanatoside C desirable for intravenous administration.[107, 215] Slowing of a rapid ventricular rate in atrial fibrillation may be effected within ten minutes to two hours after intravenous administration. As a rule its effect is maximal within 60 minutes. Its effect persists 12 to 36 hours and disappears in three to six days.[107] In summary, lanatoside C is more rapid in its effect than digitoxin, slightly more rapid than digoxin, but slower than ouabain (below). Therefore it is not as immediately effective as the latter for urgent intravenous use, but the duration of its effect is longer.

Dosage of Lanatoside C. The average oral

minute dosage required for therapeutic effectiveness. Compared to other glycosides digitoxin has a relatively long latent period. Its activity begins one hour after intravenous administration and its maximum effect requires four hours or longer. The chief disadvantage is its long period of dissipation, two to three weeks being required for elimination. Studies on radioactive digitoxin administered to patients with heart failure indicate that unchanged digitoxin is excreted in the urine for as long as 40 days after the administration of a single dose. Therefore, when toxic symptoms appear they are relatively persistent. On the other hand, the slow elimination of digitoxin may also be considered an advantage because digitalization can be readily maintained for a long time.

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Dosage of Lanatoside C. The average oral

digitalizing dose of lanatoside C is 7 5 mg (5 0 to 10 0 mg) within 24 hours[143, 307] Maintenance dose is 1 0 to 1 5 mg daily For rapid intravenous digitalization the dose is 0 8 mg to 1 6 mg lanatoside C, given slowly or in divided doses every four hours until the desired effect is attained The maintenance dose intravenously is 0 4 mg every six hours Lanatoside C is available commercially as Cedilanid in tablets of 0 5 mg and in ampules of 2 cc containing 0 4 mg and in ampules of 4 cc containing 0 8 mg See also page 263

Ouabain and Other Strophanthins

A number of glycosides have been isolated from Strophanthus kombé and Strophanthus gratus[197] The most important of these is ouabain, a pure crystalline substance derived *from the latter Both ouabain and the various* K strophanthins now available, are poorly absorbed from the gastrointestinal tract and therefore unsuitable for oral use K Strophanthoside is available commercially as Strophosid in 0 5 cc ampules containing 0 25 mg and in 1 cc ampules *containing 0 5 mg* The initial intravenous dose is 0 3 mg administered slowly to patients who have not received digitalis, and 0 15 or 0 3 mg may be given again after 24 hours

Ouabain (G strophanthin) is the drug of choice for emergency intravenous use because of its very brief latent period [redacted] A reduction in ventricular rate and venous pressure may be attained within five minutes after injection with a maximum effect in 30 to 120 minutes and a duration of 24 to 72 hours[143] *Its rapid* elimination makes ouabain unsatisfactory for *maintenance of digitalization* Therefore the combined use of ouabain intravenously for rapid immediate effect with digitalis preparations orally for subsequent maintenance has been recommended[11] *Acetylstrophanthidin* acts even more rapidly than ouabain producing its full effect in ten minutes as compared to one hour for the latter Ouabain is available in 0 5 cc ampules containing 0 1 mg, and 2 cc *ampules containing 0 5 mg* Acetylstrophanthidin is available in 1 cc *ampules* containing 0 6 mg (For dosage and administration of ouabain and acetylstrophanthidin, see p 262)

Other Digitalis like Preparations—Squill

Glycosides of squill also have a satisfactory digitalis like action and have been used therapeutically The commercial preparation Scillaren contains 2 parts *crystalline scillaren* A and one part of amorphous scillaren B One commercial preparation urginin (Urginea Indica) has two water insoluble glycosides urginin A and B, while another urginin (from Urginea Maritima) contains equal mixtures of scillaren A and B The digitalizing dose is 9 0 to 14 0 mg for scillaren and 4 0 to 6 0 mg for urginin The daily maintenance dose is about 0 8 mg for urginin and 1 6 mg for scillaren

Still other preparations with a digitalis like action, but not recommended for clinical use *include cymarin from apocynum, thevetin, a* cardiac glycoside obtained from the nuts of the be-still plant, convallaria, and folinerin—a crystallized glucoside from the Nerium oleander Analyses of the various commercial *preparations and their therapeutic effects* have been reported by Stroud and Vander Veer,[323] De Graff[85] and Freedberg and Zoll[130]

STANDARDIZATION AND ASSAY OF DIGITALIS PREPARATIONS

According to U S Pharmacopoeia XIV the potency of digitalis is such that when assayed as directed 0 1 gm shall be equivalent to not less than 1 0 U S P digitalis unit One U S P digitalis unit represents the potency of 0 1 gm of the U S P Reference Standard This latter in turn is standardized according to a standard international reference powder of digitalis of the World Health Organization of the United Nations In actual usage digitalis preparations for intravenous injection con*taining a given number of digitalis units may* have a much greater pharmacologic effect than digitalis leaf preparations with the same number of units administered orally This is largely due to less and variable absorption from the gastrointestinal tract of the oral preparations

The pure glycosides such as digoxin and digitoxin are standardized by weight with the aid of *colorimetric techniques Digitalis leaf* preparations are assayed by biologic tests Formerly the frog method was official, a frog unit being defined as the amount of digitalis per gram of frog weight, which when injected into the ventral lymph sac of male frogs (20 to 30 gm) produced permanent systolic stand still in one hour at room temperature Later the cat method was used The amount of *dissolved drug, injected intravenously*, necessary to cause cessation of the cat's heart beat was compared with the amount of the

standard necessary to produce this lethal effect At present pigeons are employed for assay, the material tested being compared with a standard preparation as to the quantity necessary to produce fatal cardiac arrest on intravenous administration The potency of the assayed preparation is expressed in U S P units per cc

This method of assay is far from ideal and does not accurately and consistently measure the effect of the drug as given to humans by mouth and in therapeutic doses as contrasted with its assay in animals given intravenously and in lethal doses Gold[141] showed that a variety of digitalis preparations of identical potency in cat units exhibited a ten fold range of activity in humans Assay in humans by electrocardiographic modification has been attempted but is still unsatisfactory [339] Chemical and colorimetric assays have likewise failed to yield consistent results or reliable measurements of therapeutic activity in humans [78]

THE ADMINISTRATION OF DIGITALIS

Modern concepts of adequate digitalis dosage are based on the detailed studies of Eggleston[95] with standardized digitalis preparations For a long time inadequate doses were utilized with unsatisfactory effects despite Withering's[345] admonition that the drug be continued until it acts either on the kidneys the stomach the pulse or the bowels let it be stopped upon the first appearance of any one of these effects On the other hand it is usually possible to obtain a satisfactory therapeutic effect without quite causing the symptoms mentioned by Withering for these symptoms are evidences of overdosage *The fundamental principle of digitalization is to administer the drug until the desired therapeutic effect is achieved or toxic symptoms appear* But it is rarely necessary to induce toxic manifestations

Choice of Digitalis Preparation

Effective digitalization can be attained by any of the preparations listed The physician should be thoroughly familiar with at least one preparation for intravenous use in order to obtain very rapid digitalization and one preparation for oral slower action At present there is ouabain or Cedilanid for intravenous use gitalin digoxin digitoxin or digitalis leaf for oral use Intravenous administration has no more beneficial effect on myocardial function than oral administration Neither is one oral preparation more effective than another when the proper dosages are administered The essential differences concern the speed of action and the time required for dissipation and elimination

The technique of administering digitalis includes (1) the induction of digitalization rapidly or slowly until the desired therapeutic effect is obtained without symptoms of overdosage and (2) subsequent maintenance of digitalization so that the benefits of the drug are retained continuously as long as necessary

Methods of Inducing Digitalization (Oral Methods)

Although the total dose necessary to obtain a maximum therapeutic effect without toxic symptoms varies from patient to patient and even in the same patient at different times Eggleston[95] has shown that this dose can be predicted approximately from the weight of the patient Allowance must be made for the amount of digitalis eliminated or destroyed by the body during the period in which digitalization is induced Therefore a larger total dosage is required to digitalize a patient in one or two weeks than to digitalize him in one or two days

In practice we have learned the approximate oral digitalizing dose for the various digitalis preparations and this amount is given in single or divided amounts within the period to be allowed for digitalization

The average digitalizing doses (within 24 to 48 hours) for the commonly employed digitalis preparations are

Oral	*Average*	*Usual Range*
Digitalis leaf	1 8 gm	1 2 to 2 0 gm
Tincture of digitalis	18 cc	12 to 20 cc
Digitoxin	1 8 mg	1 2 to 2 0 mg
Digoxin	3 75 mg	2 0 to 5 0 mg
Gitalin	5 5 mg	3 to 10 5 mg
Lanatoside C	7 5 mg	5 to 10 mg

Very large persons may require more and small or aged persons somewhat less Larger doses of digitalis than the above-stated average may be necessary to attain a satisfactory therapeutic effect in patients with very severe congestive heart failure and when failure is associated with active rheumatic fever infections or hyperthyroidism Children above the age of four have been found by McCulloch and Rupe[23] to require considerably more digitalis per body weight than the

doses given above for adults; Sutton and Wyckoff[34] however, found no essential difference in their study on the treatment of children with rheumatic heart disease (See p 261 for digitalization in children)

The important point to remember is that the above doses are practical average figures which may require considerable modification in individual cases Much larger doses may have to be administered if a satisfactory therapeutic effect is not obtained or the drug may have to be stopped before the full estimated dose is given if more than mild symptoms of digitalis intoxication appear Two weeks are usually required for the elimination of digitalis from the body If digitalis has been administered in the preceding two weeks and further digitalization appears necessary the amount remaining may possibly be calculated and subtracted from the dose that would have been given if the patient were digitalis free But if there is any doubt it is safer to digitalize slowly by administering digitalis leaf powder 0 1 gm every six hours and observe the patient carefully for therapeutic or toxic effects Because of their speedier elimination lanatoside C (Cedilanid) 1 mg three times a day or digoxin 0 5 mg three times a day may be preferable in these circumstances

The speed with which digitalization is induced depends on the urgency of the patient's clinical condition The following oral methods have been found practical but they may be modified

Rapid Digitalization in 12 to 36 Hours This method applies to patients with acute congestive heart failure especially when caused by a paroxysm of atrial fibrillation with extremely rapid ventricular rate, to patients with acute left ventricular failure and to patients with severe chronic congestive heart failure When digitalization is required within four hours or less intravenous therapy should be employed (p 262) However Evans et al[115] have found 2 to 3 mg of digoxin, given orally satisfactory for digitalization in four hours Rapid oral digitalization may also be effected by digitoxin A single dose of 1 5 mg often effects digitalization in six hours but this initial dose may produce toxic symptoms It is important to avoid rapid digitalization when slower methods suffice as they do in the vast majority of cases of heart failure The following table represents the usual initial and subsequent doses for rapid digitalization (24 hours) with various digitalis preparations

Oral	*Initial dose*	*Dose every 8 hours thereafter until digitalization*
Digitalis leaf	0 8 gm	0 2 gm
Digitoxin	0 8 mg	0 2 mg
Digoxin	1 5 mg	0 5 mg
Gitalin	2 5 mg	0 75 mg
Lanatoside C	3 0 mg	1 0 mg
Tincture of digitalis	8 0 cc	2 0 cc

Digitalization in Three Days This method is useful for patients with well developed but not urgent signs of congestive heart failure Digitalization can be accomplished fairly rapidly at the same time that toxicity is more readily avoided because it is easier to stop short of excessive dosage A dose of 0 2 gm of powdered digitalis leaf (or 0 2 mg digitoxin or 0 5 mg digoxin or 0 75 mg gitalin) is given three times daily for two or three days If the rapidly excreted digoxin or lanatoside C is used it is preferable to give the total daily dose in the morning instead of dividing it into three doses per day Thereafter dosage is determined by therapeutic effect or the development of toxicity

Slow Digitalization in One Week This method is practical for mild or moderately decompensated patients for ambulant patients examined only in the office or hospital outpatient department who are not likely to be seen oftener than once a week, and for patients with uncertain amounts of unexcreted digitalis Either 0 1 gm of powdered leaf or 1 cc of the tincture is given three times daily or 0 3 mg digitoxin or 0 75 mg of digoxin or 1–1 5 mg of gitalin or 1 5 mg of lanatoside C is given in a single daily dose until the desired therapeutic effect is achieved or toxic manifestations supervene Many patients will require continuation or elevation of this dosage, as determined by the clinical status at the end of a week In other cases the dosage may be reduced to the level necessary for maintenance

Criteria of Therapeutic Effect Having carried out one of the above schedules of dosage the physician must determine whether satisfactory digitalization has actually been attained i e, whether the patient has had a maximum therapeutic response If not and regardless of the dosage already administered, the recommended dose of digitalis

should be continued until adequate benefit is secured or toxic symptoms appear

In patients with atrial fibrillation and a rapid ventricular rate slowing of the heart and elimination of a pulse deficit are approximate criteria of favorable digitalis effects As a rule the heart rate is slowed to 70 to 80 per minute but some patients are comfortable only if the resting cardiac rate is slowed to about 60 for it may rise considerably with slight activity On the other hand it is not safe to continue digitalis until such slowing is obtained without regard to other manifestations for digitalis intoxication may occur while the heart rate is still relatively rapid However even slower rates may be safely achieved if there are no toxic signs or symptoms Furthermore a rapid pulse rate may be misleading when due to ventricular extrasystoles resulting from digitalis intoxication For the rapid rate may be interpreted as indicating that the patient's condition is worse and that he is in need of larger doses of digitalis Therefore the cardiac and pulse rates are guides to the administration of digitalis only when considered in connection with the patient's clinical course as regards both the symptoms of heart failure and those of digitalis overdosage (p 264)

In patients with regular rhythm a satisfactory therapeutic effect of digitalis is indicated by relief of dyspnea orthopnea or cardiac asthma by diuresis and loss of edema disappearance of rales at the bases of the lungs and a diminution in the venous pressure and circulation time Although there is no doubt of the benefit of digitalis in heart failure with regular sinus rhythm its therapeutic accomplishment is rarely as striking as in heart failure with atrial fibrillation and a rapid ventricular rate I therefore rarely use intravenous digitalization in patients with sinus rhythm and try to avoid haste and excessive dosage For one is most apt to induce digitalis toxicity in these patients with sinus rhythm because the clinical criteria for digitalization are more difficult to evaluate than the criterion of ventricular rate in cases with atrial fibrillation Persistence of the clinical manifestations of heart failure is commonly due to the complicating factors or incomplete or improper use of other therapeutic agents and not necessarily to inadequate digitalization Therefore one should be very cautious in pressing digitalization after one has administered an average dose in patients with sinus rhythm

Maintenance of Digitalization

When the optimal response has been obtained it is important to maintain a continued state of therapeutic digitalis saturation by administering smaller doses of medicament to compensate for the amount excreted or destroyed by the body According to Gold and De Graff[14] the patient does not excrete a fixed amount of drug each day but a fraction of the amount present in the body Thus 0 2 gm of digitalis may be excreted daily and may have to be administered daily to maintain digitalization after the patient has been digitalized with 1 5 gm of digitalis leaf However if the patient has received no digitalis previously a daily dose of 0 2 gm may be cumulative and eventually effect digitalization

In practice the daily maintenance doses for the common digitalis preparations are

Digitalis leaf	0 1 gm (0 05 to 0 15 gm)
Tincture of digitalis	1 0 cc (0 5 to 1 5 cc)
Digitoxin	0 1 mg (0 05 to 0 2 mg)
Digoxin	0 25 mg (0 125–0 75 mg)
Gitalin	0 5 mg (0 25–1 0 mg)
Lanatoside C	1 0 mg (0 5–1 5 mg)

As with the initial digitalizing dose the maintenance dose must be adjusted to the individual and his clinical response The above doses are approximations to be used as guides It should be emphasized that most patients with congestive heart failure will require maintenance doses of digitalis for the balance of their life

If symptoms of digitalis intoxication appear either during the induction or maintenance of digitalization the drug should be discontinued until the toxic symptoms disappear and for one to two days thereafter Digitalis may then be resumed in smaller dosage It should be recognized however that in patients with severe congestive heart failure the optimal therapeutic and the toxic dose are sometimes very close In ambulant patients with mild congestive heart failure there is a wide margin between the therapeutic and toxic doses and an optimal clinical result should be obtained with smaller doses and therefore without toxic symptoms[15]

Digitalization of Children

Heart failure in children is usually due to rheumatic fever and rheumatic cardiovalvular

disease, occasionally to congenital heart disease Persistent rheumatic activity with acute and subacute carditis is the rule in the rheumatic cases of heart failure and this prevents or obscures the therapeutic efficacy of digitalis This may be the reason for the frequent statement that children require 50 to 100 per cent more digitalis per pound of body weight than do adults[2] Similarly pronounced arterial anoxemia in children with congenital heart disease and heart failure impairs the therapeutic action of digitalis On the basis of the dosage of digitalis producing RS-T wave changes in the electrocardiogram Mathes and associates[30] found that children were more tolerant to digitoxin than were adults when the digitoxin was given orally in the same dose per unit weight But the differences appeared small and of questionable practical significance Nevertheless the authors concluded that children required about 50 per cent more digitoxin by body weight than adults Crawford et al[72] suggested that digitalis dosage should be determined according to surface area, and explained the higher digitalis dosage required by children as due to a relatively larger surface area per unit of weight

To avoid the toxic symptoms which occur with disproportionate frequency in digitalized children, very rapid digitalization should be shunned, and dosage should be gauged by therapeutic effect rather than by arbitrary calculation For children weighing between 50 and 100 pounds one-half the adult dose may be used as an approximate amount for initial digitalization, below 50 pounds one sixth to one quarter the adult dose should be given Taussig[7] recommended digitalization by administering 0 1 gm (1½ grains) of digitalis leaf three times daily until optimal therapeutic effect is obtained or toxic symptoms appear She then advised a maintenance dose of 0 05 to 0 1 gm (¾ to 1½ grains) daily, with complete omission of the drug for one or two days each week Rosenbaum and associates[240] administered 0 02 to 0 025 mg digitoxin per pound to children more than two years of age and 0 01 to 0 02 mg to children less than two over a period of 24 hours for digitalization, or more rapidly in emergencies One tenth of the digitalizing dose was given daily orally for maintenance of digitalization Using this dosage schedule in 41 infants and children in congestive heart failure Nadas et al[25] observed the most satisfactory response when the heart failure was due to myocardial disease, paroxysmal tachycardia or rheumatic carditis and the least satisfactory when it was due to congenital heart disease especially with cyanosis If the above mentioned dosage schedule is used with other digitalis preparations, the following equivalents may be useful approximations 0 1 gm digitalis leaf, 0 1 mg digitoxin, 0 25 mg digoxin, 0 5 mg gitalin For emergency digitalization of children Cedilanid may be given intravenously but slowly in a total dose of 0 02 mg per pound body weight or in fractional doses provided no digitalis has been given in the previous two weeks

Intravenous Administration of Digitalis or Strophanthin (Ouabain) Intramuscular Digitalization

The intravenous administration of digitalis is indicated only in emergencies requiring digitalization within a few hours This might be necessary for patients with acute congestive heart failure due to an attack of paroxysmal atrial fibrillation with very rapid ventricular rate, patients with acute congestive heart failure or myocardial infarction and massive pulmonary edema, undigitalized patients with chronic congestive heart failure who are moribund, or in patients developing heart failure during operations[153] As a rule however sufficiently rapid digitalization can be obtained by the oral route Sometimes intravenous digitalization is employed when the patient cannot take oral medication because of vomiting, as in patients who have recently undergone surgery, or because of coma Ouabain or digitalis preparations should not be given intravenously if the patient has received a digitalis preparation in the preceding two weeks In general the intravenous administration of digitalis or strophanthin is rarely essential If there is no emergency but digitalis must be administered parenterally because the patient cannot take oral medication, digitoxin and other digitalis preparations may be administered intramuscularly[2,1] The dose time of onset and peak action of intravenously administered digitalis and strophanthin preparations are shown in Table 8

When intravenous digitalization is necessary, ouabain, the crystallized glycoside from

Table 8 Dosage and Time of Action of Intravenously Administered Digitalis Glycosides

DRUGS	INITIAL DOSE mg	ONSET OF ACTION	PEAK ACTION	REGRESSION AND DISSIPATION
Acetylstrophanthidin	0.3–0.6	1–5 min	10–15 min	4 hr
Ouabain	0.25–0.5	3–10 min	½–2 hr	12 hr–3 days
Strophanthin K (Strophosid)	0.3–0.6	10–15 min	1–2 hr	1–5 days
Lanatoside C (Cedilanid)	0.8	10–30 min	1–3 hr	1–6 days

Note Total digitalizing dose is usually twice the initial dose

G strophanthus is preferred to digitalis preparations because of its more rapid action (five to forty five minutes as compared to two or three hours) Furthermore the effect of ouabain is dissipated more rapidly (one to two days as compared to one to three weeks for digitalis) There has been some fear of using strophanthin and ouabain which are powerful poisons (used long ago as arrow poisons) and which can produce premature beats ventricular tachycardia or fibrillation and death within a half hour after injection But it is doubtful whether the relation of therapeutic to toxic dose for ouabain is different from that of the digitalis glycosides Most of the reported accidents may have been due to previous digitalization with incomplete elimination at the time ouabain was injected or to overdosage

Wyckoff and Goldring[307] administered ouabain intravenously in patients with atrial fibrillation and rapid ventricular rate with good therapeutic results and without dangerous incidents The full therapeutic dose was found to be 1 mg for 150 pounds of body weight *A total dosage of 1 mg of ouabain should not be exceeded in a 24 hour period* *It should not be given at all if digitalis has been administered in the preceding two weeks* Wyckoff and Goldring[307] gave an initial dose of 0.5 mg followed by injections of 0.1 mg every half hour until a satisfactory therapeutic or toxic effect was obtained A maximum action was usually observed in less than an hour Slowing of the heart thus obtained persisted for five days or less While I have found this dosage schedule to be a safe one some physicians prefer to proceed more cautiously with an initial dose of 0.25 mg of ouabain followed by injections of 0.1 mg at half hour intervals until effective The drug should be administered slowly Another procedure is to give 0.25 to 0.5 mg of ouabain intravenously in a single dose and simultaneously 0.6 mg of digitoxin or 1.5 mg of digoxin orally to continue digitalization or digitalis leaf can be given in 0.2 gm doses every six hours until digitalization is effected According to this regime the intravenous injection is utilized only for a speedy start but is not repeated If digitalization is effected intravenously and no further digitalis is given for several days it is not necessary to repeat digitalization provided the therapeutic effect has persisted One may maintain digitalization with ordinary maintenance doses Although the intravenous drug is rapidly dissipated its therapeutic effect may persist several days longer

Acetylstrophanthidin is a partial synthetic which has almost an immediate digitalis like action Its full effect is attained in 10 to 15 minutes and wears off in four to five hours There is some question as to the difficulty in controlling its dose and the consequent danger of toxicity[316] There are several reports as to the value of this drug[107, 153] but the occurrence of ventricular fibrillation has been noted following its administration[61] It is about half as potent as ouabain and its digitalizing dose is 1 to 2 mg The initial dose is 0.6 mg intravenously administered very slowly and 0.2 mg at 20 to 30 minute intervals until digitalization is effected

Of the various digitalis preparations probably lanatoside C is the most desirable for intravenous use because it is a pure crystalline substance of constant composition and because it has the briefest latent period and the most rapid rate of elimination of the commonly available digitalis glycosides Lanatoside C is marketed as Cedilanid in 2 cc and 4 cc ampules containing *0.2 mg per cc* Sokolow and Chamberlain[307] used it in doses up to 14 cc per day in 38 cases In general 8 cc was the digitalizing dose and [illegible] to 14 cc in

24 hours in divided doses digitalized most patients In practice one may inject 4 cc (0 8 mg) repeat in four hours and thereafter give 2 cc (0 4 mg) every six hours as indicated In cases of atrial fibrillation the ventricular rate sometimes falls to 40 or 50 within thirty minutes to two hours Maintenance doses of digitalis should be continued orally if possible after digitalization has been effected Digoxin gitalin[163] and digitoxin may also be given intravenously but have progressively longer latent periods than Cedilanid in the order named

Other commercial solutions of digitalis, provided in sterile ampules for intravenous injection are available for example digalen *digifoline or digitan According to Pardee* [80] a safe and satisfactory initial dosage is 6 to 8 cat units (0 45 to 0 60 mg) administered slowly If a satisfactory clinical result is not obtained within two or three hours a second injection of 2 cat units (0 15 gm) may be given and repeated again if necessary in three hours Slowing of the heart may occur within fifteen minutes but the maximum effect usually appears two to three hours after the injection and persists for 12 to 24 hours Digitalis should not be given intravenously if the patient has received digitalis in the preceding two weeks Often after the initial dose digitalis therapy can be continued orally in doses of 0 2 mg every six hours until the desired effect is obtained The above solutions have been administered in similar dosage intramuscularly or hypodermically when a vein cannot be entered and urgent digitalization is required

Rectal Administration of Digitalis

Digitalis may be administered rectally[21] to patients who cannot take oral medication because of nausea and vomiting due to congestive heart failure or to other causes but is now rarely used

EVIDENCES OF DIGITALIS OVERDOSAGE

Toxic manifestations are an essential feature of overdosage with any effective preparation of digitalis or of a drug with digitalis like action Claims that a given preparation of digitalis never produces such toxic symptoms are either untrue or indicate the inertness of the preparation concerned Patients differ greatly in their tolerance to digitalis consequently some present toxic symptoms with doses which are ordinarily considered inadequate therapeutically In some patients especially those with very severe congestive heart failure, the toxic and therapeutic doses are almost identical and it is difficult to obtain satisfactory clinical improvement without evoking mild and recurrent toxic symptoms

The occurrence of digitalis toxicity may be related to potassium metabolism Depletion of potassium sensitizes the myocardium to digitalis and induces toxicity with doses of digitalis which are ordinarily non toxic[218] Thus digitalis poisoning is likely to be induced in conditions associated with potassium loss due to vomiting, diarrhea, mercurial diuresis especially when mercurials are administered in association with ammonium chloride steroid therapy (cortisone or ACTH) or during treatment of diabetic ketosis with insulin and glucose These conditions are most apt to deplete the body of potassium when the dietary intake of potassium is diminished because of anorexia nausea or vomiting or other reasons Most often the body potassium depletion is not clearly reflected in the plasma potassium which remains within the normal range

Among other causes of digitalis toxicity besides unexplained grossly excessive dosage are the neglect of warnings of early poisoning and too vigorous exhibition of digitalis to the neglect of other measures in an effort to obtain a therapeutic effect Not infrequently digitalis toxicity occurs when there was no rational indication for the use of this drug[82]

The most common evidences of overdosage with digitalis are those representing (1) *gastrointestinal disturbances* and (2) *disturbances in cardiac rhythm*

Anorexia Nausea, Vomiting

Nausea and vomiting are the commonest early symptoms of digitalis overdosage Usually these are preceded for a day or two by moderate or complete anorexia When the latter is noted after an average therapeutic dose of digitalis the more annoying vomiting may be prevented by prompt discontinuance of the drug The vomiting is of central not of gastric origin for it appears even after intravenous injections of digitalis[170] and in animals nausea and vomiting movements were induced by Hatcher and Eggleston[169] following the administration of digitalis even when the gastrointestinal tract had been removed (However, local gastric irritation can result from large initial dosage of whole leaf tab

lets) Whether the vomiting results from direct stimulation of the vomiting center in the medulla or by a reflex from the heart is still a controversial question

The chief practical problem presented by the appearance of nausea and vomiting during the administration of digitalis is to determine whether these symptoms are due to the drug which would demand its discontinuance or to uncontrolled congestive heart failure (p 293) which would require continued or increased dosage Unfortunately for such decisions some patients as shown by Eggleston [89] vomit after only one half to two thirds of the usual digitalizing dose while others require as much as 8 o gm before vomiting appears If a beneficial therapeutic result has been obtained o if the dose administered is nearly equal to the amount estimated for digitalization it is best to discontinue the drug for one to three days and then resume it in smaller doses If less than two thirds of the estimated dose has been given when vomiting appears if there are no other toxic symptoms (such as bigeminal rhythm) and if the symptoms of congestive heart failure are still uncontrolled it is preferable to continue the digitalis despite nausea and vomiting with careful observation for the possible development of other toxic manifestations of the drug Nausea and vomiting in patients with congestive heart failure are often due not only to the congestive failure itself but also to other factors These symptoms frequently subside if food fluids and medication by mouth are eliminated for a brief period while sedatives are administered and digitalis is continued intravenously or rectally

Diarrhea was noted by Withering[356] as a consequence of digitalis but this is uncommon except with very excessive doses However when this symptom appears during digitalis medication the possibility that it represents intoxication with the drug must be considered Other evidences of digitalis overdosage will be found if this is the case

Cardiac Disturbances

Cardiac arrhythmias have occurred with increasing frequency since the use of the pure cardiac glycosides especially digitoxin This may be due to the recommended and widely accepted excessive maintenance dose of 0 2 mg of digitoxin daily but the slow cumulative action and delayed excretion of this drug may also contribute to its toxicity It is particularly noteworthy that the cardiac disturbances may be induced by digitalis toxicity without preceding or concomitant telltale gastrointestinal disturbances and even without the classic ST T effects of digitalis on the electrocardiogram

Premature Beats and Bigemini Next to the gastrointestinal symptoms premature beats (extrasystoles) are the commonest manifestations of digitalis overdosage A characteristic form of premature beats associated with digitalis overdosage is that termed *bigemini* an arrhythmia in which every normal beat is followed by a premature contraction (Fig 57) Various premature beats including bigemini also occur in patients who have not received digitalis When such patients are in heart failure digitalis is not contraindicated and the medicament may actually eliminate the premature beats When however bigemini first appear during full digitalization they must be interpreted as an evidence of overdosage and the digitalis should be interrupted for at least a day after they disappear If the premature beats (isolated or in bigeminal rhythm) are due to digitalis they are almost always of ventricular type and vary in electrocardiographic configuration because they are of multifocal origin [33] Sometimes alternating left and right ventricular premature beats are seen with



Fig 57 Digitalis intoxication Bigemini due to regularly recurrent ventricular premature beats

toxic doses of digitalis In patients with atrial fibrillation, the presence of bigemini may still be recognizable by the coupling of the pulse produced during the periods of extrasystoles but often electrocardiograms are necessary for their discovery in such cases Electrocardiographic observation is essential powdered leaf Usually, however they appear after an adequate therapeutic dosage

Disturbances in Conduction *Excessive slowing of the pulse* is another evidence of digitalis overdosage Usually the drug should be discontinued if the heart rate falls below 60 per min and almost always if it falls below 50

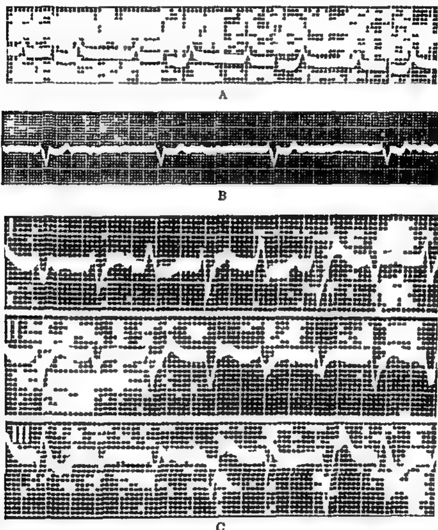


Fig 58 Digitalis intoxication

A Prolonged P R interval and S-T depression Lead II

B Atrioventricular dissociation Idioventricular pacemaker with regular rhythm despite atrial fibrillation Complete heart block Lead II

C Ventricular tachycardia of multifocal origin

to discover toxic cardiac disturbances when ever digitalization is being effected when digitalis dosage is being changed, and from time to time as the maintenance dose is established While extrasystoles in animals occur only after huge doses (50 to 75 per cent of the lethal dose) in man they may appear after only three or four doses of 0 1 gm of the

Various grades of partial *heart block* or complete heart block occur (Fig 58) McGuire and Richards [33] reported the development of complete heart block in the normal heart of a person who took 30 gm of digitalis with suicidal intent In a series of 71 cases of complete heart block studied by Ide [111] digitalis was responsible in 12 In patients

with congestive heart failure digitalis often causes partial heart block due to impairment of atrioventricular conduction But this may occur occasionally even with therapeutic doses If such dosage is not exceeded digitalis may be administered to patients who already show partial heart block without increasing the delay in conduction

Disturbances in Sinus Rhythm and Sinoatrial Conduction By its vagal action toxic doses of digitalis may depress sinoatrial impulse formation or sinoatrial conduction As a result digitalis may induce sinus arrhythmia sinus arrest [111] sinoatrial block [16] and atrial standstill By a similar mechanism of sinus depression digitalis intoxication may evoke atrioventricular nodal rhythm nodal tachycardia [311] nodal rhythm with atrioventricular dissociation and interference beats (Fig 59) These arrhythmias are discussed in Chapters 13 14 and 15



Fig 59 Interference dissociation due to digitalis intoxication Ventricular rate 120 atrial rate 115 per minute Third and tenth ventricular complexes (interference beats) are responses to conducted sinus impulses

Atrial Fibrillation and Tachycardias *Atrial fibrillation* is frequently induced by therapeutic doses of digitalis in patients with atrial flutter (p 357) However this and rarely *atrial flutter*[111, 43] *may develop in* hearts with normal rhythm after toxic doses of digitalis [271, 43] *Tachycardia* as well as ex*cessive slowing of the heart may represent* digitalis intoxication This may be due to numerous ventricular extrasystoles which result *from excessive digitalis (Fig 58C) If* the toxic significance of the tachycardia is unrecognized and digitalis therapy continued *paroxysmal ventricular tachycardia* may result [131] Ventricular fibrillation may be a possible consequence of overdigitalization[108] *and may account for cases of sudden death* due to intravenous strophanthin Enselberg and associates[109] and Burrell and Coggins[51] *reported cases of ventricular fibrillation fol*lowing the intravenous administration of acetylstrophanthidin In humans who were *subject to attacks of ventricular fibrillation* Schwartz and Jezer[285] were able to precipitate *such paroxysms with digitalis*

Other arrhythmias have also been occasionally evoked by toxic doses of digitalis *These include electrical and pulsus alternans* and paroxysmal atrial tachycardia with or without [illegible] block [177] The latter was induced repeatedly even with small doses of digitalis In the past few years the occurrence of paroxysmal atrial tachycardia with block as a manifestation of digitalis toxicity has been reemphasized [17, 16] It may be mistaken for atrial fibrillation or impure flutter and erroneously lead to increased digitalis dosage When this arrhythmia occurs in patients with heart failure treated with digitalis it often appears to be related to potassium depletion and its elimination may be hastened by the administration of potassium as well as by discontinuing digitalis *A rapid* ventricular rate associated with atrial fibrillation and overdigitalization may be slowed by the administration *of potassium (Fig 60)*

Treatment of Toxic Arrhythmias due to Digitalis or Strophanthus. Digitalis is discontinued until several days *after all signs of toxicity are* abolished Therapy of digitalis induced arrhythmias has been advanced by the use of *procaine amide (Pronestyl) (p 350) and by* the administration of potassium salts (p 341) The benefit of potassium salts in the *control of ectopic cardiac rhythms has long* been known [61] Now it has been found especially valuable to reduce myocardial irri*tability specifically* due to digitalis by restoring myocardial potassium depleted by digitalis [281, 111, 311] Sampson and associates[234] eliminated digitalis induced extrasystoles with 5 to 10 gm of potassium acetate in a 25 per cent solution The response was usually obtained in 40 minutes and persisted three to eight hours In addition to the specific use of potassium Pronestyl quinidine and other agents may be used to control the various

types of cardiac arrhythmias due to digitalis, just as they would be employed in the therapy of the same arrhythmias due to other causes Magnesium has been found effective in abolishing extrasystoles bigemini and ventricular tachycardia caused by digitalis [2] Many of

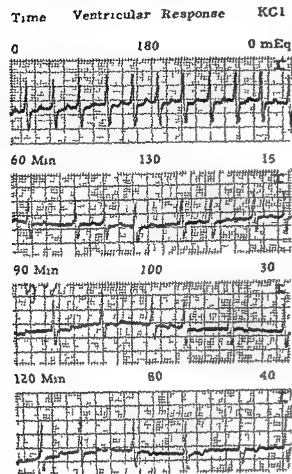


Fig 60 Atrial fibrillation associated with digitalis toxicity treated with potassium Following maintenance on 0 3 gm of digitalis leaf daily for three months patient experienced a paradoxical increase in ventricular rate with regularization of R R interval after a profuse mercurial diuresis (with loss of potassium) Ventricular rate slowed progressively within two hours after intravenous administration of 40 milliequivalents of potassium chloride in 5 per cent glucose in distilled water (Courtesy Dr Marvin Bachner)

the arrhythmias induced by digitalis and many of the other manifestations of digitalis toxicity resemble similar disturbances due to the underlying cardiac disease or heart failure and the problem arises whether to discontinue digitalis or whether the findings actually denote that the patient has not been adequately digitalized. Sometimes a careful history reveals that the manifestations which might be attributed to digitalis were present before digitalis was begun, or at a time when the dose of digitalis was too small to be considered causal On the other hand, if there is any doubt it is preferable to discontinue digitalis for a few days or longer if the symptoms appear to improve or not to worsen At the same time all other measures for treating heart failure are utilized But if it becomes apparent that the symptoms were not due to digitalis digitalization can be effected rapidly

Nervous and Other Symptoms

Headache is relatively common with excessive digitalization Occasionally visual blurring scotomata or colored vision (green and yellow) is produced [276] Weakness and mental disturbances are not uncommon especially in elderly patients Despite the criteria set down by Carr[35] for attributing mental or psychotic disturbances to digitalis overdosage, it is often difficult to distinguish such a relationship for the symptoms in cases which I have observed could also be attributed to rapid or excessive dehydration caused by restriction of fluid and salts, and especially to the diuresis produced by mercurial salts [341] I have observed similar symptoms following excessive diuresis in patients with heart failure who have received no digitalis Batterman and Gutner[17] described unusual neurologic manifestations of digitalis toxicity in 10 patients, characterized particularly by neuralgia of the lower third of the face mandible or maxilla and by pain in the upper extremities lower lumbar and calf muscles Mental symptoms may also be due to advanced heart failure per se or to associated renal insufficiency

Other Toxic Effects

Eosinophilia attributed to marked vagotonia caused by digitalis, has been noted by several observers [77, 178] Allergic disturbances such as urticaria[358] have been described [88] Dangerous and sometimes fatal results have been reported as resulting from the combined or successive administration of digitalis and other drugs especially ephedrine[188] and calcium [307] When dealing with patients with heart failure however one must be cautious in attributing sudden death to an extraneous factor

Increasing Cardiac Failure or Intractable Heart Failure

Overdigitalization sometimes appears to be responsible for increasing cardiac failure or

for heart failure becoming intractable and refractory to treatment. Whether this represents some direct toxic effect on the myocardium or whether the effect is due to electrolyte disturbance (potassium depletion) is uncertain. There is evidence that digitalis and ouabain drive potassium out of the heart muscle cells and possibly deplete their energy rich phosphates.[254] In practice one should investigate the possibility of overdigitalization in every patient with intractable heart failure.

Thrombotic Effect of Digitalis

There have been claims that digitalis increases the coagulability of the blood, but this has been disputed.[11] The importance of this question lies in the purported tendency of digitalis to promote fatal embolization. This danger has been particularly emphasized in cases of acute myocardial infarction in which digitalis has been employed.

Pathologic Myocardial Lesions

After large toxic doses of digitalis given to animals, microscopic examination reveals areas of focal necrosis, vacuolization or dissoluton of muscle fibers, hemorrhages, cellular infiltration and fibrosis.[19] Kyser and his associates[202] called attention to the similarity of these anatomic abnormalities to those caused in dogs by vagal stimulation or injections of acetylcholine. These similarities and their own experimental observations led them to conclude that the cardiotoxic effect of digitalis in the dog is due to vagal stimulation which causes coronary vasoconstriction. Atropinization or drugs causing coronary vasodilatation (aminophylline, theobromine) diminished the lesions produced by digitalis. Digitalis induced myocardial lesions have been reported in the presence of experimental hyperthyroidism in cats.[84]

THE EFFECT OF DIGITALIS ON THE ELECTROCARDIOGRAM

It is extremely important to be familiar with the electrocardiographic changes caused by digitalis because some are characteristic of the drug and others may be indistinguishable from the changes caused by myocardial disease, especially that due to coronary arteriosclerosis and occlusion. Digitalis has been employed by persons with normal hearts in order to mislead their physicians into making a diagnosis of myocardial disease with the aim of illicitly collecting disability insurance. The electrocardiogram is useful in discovering or confirming the presence of cardiac changes due to digitalis overdosage.

The earliest and most important electrocardiographic effects of digitalis are on the RS-T interval and T wave (Fig. 58-1). These occur in persons with normal as well as diseased hearts. They occur before full therapeutic benefits are obtained and therefore are no indication for discontinuing the digitalis.

A depression of the RS-T interval followed by an inversion of the T waves is the characteristic change of digitalis[64, 114, 111] (Fig. 58A). Shortening of the Q-T interval and lowering of the T wave[111] are also early effects of digitalis. The exact changes encountered differ somewhat in normal hearts and in those which showed electrocardiographic alterations before digitalis was begun. In *normal hearts* the chief effect is on the RS-T interval, the changes in the T wave being secondary to the displacement of the origin of the RS-T interval. The ST level first becomes depressed so that it begins below the isoelectric line and forms a curve which is concave upward. Later the S-T interval, starting below the isoelectric line, turns sharply downward and then forms a right angle as it turns up again to join the T wave. Finally the upward (second) limb of the ST segment turns up more sharply so as to form an acute angle. There is no true inversion of the T wave since its peak is still above the isoelectric line, but the changes in the S-T interval make the T wave appear either inverted or diphasic. Another characteristic is the slow downward slope from the peak of the T wave so that it hardly reaches the baseline when it joins the next P wave. These changes in the S-T interval and T wave are characteristic of digitalis and should not be mistaken for the T waves caused by myocardial disease.

In *diseased hearts* whose T waves were originally upright, the ST changes with digitalis are often indistinguishable from those in normal hearts. Frequently, however, digitalis produces alterations in such hearts which are indistinguishable from those due to myocardial damage secondary to coronary artery disease. There is a distinct ST segment depression which may be convex upward and a pronounced inversion of the T wave.

If, however, the T waves are inverted in all leads before digitalization, they usually become less inverted after digitalization, or the

S-T interval may become depressed without significant change in the T waves On the other hand if there is only slight inversion of the T waves before digitalis the drug may increase the negativity of these waves Occasionally negative T waves are rendered upright by digitalis In cases with left axis deviation with upright T waves the S T interval in lead I may become depressed and T_1 inverted while ST_3 becomes elevated and T_3 upright thus resembling the changes seen in anterior myocardial infarction

In the precordial leads Strauss and Katz[3 9] observed a depression or elevation of the S T interval and diminution in the size of the T wave Rarely the T wave disappeared or became inverted RS T segment deviations and T wave abnormalities in the precordial leads may simulate those due to coronary occlusion with myocardial infarction[319] Beers et al[16] found the most striking digitalis changes in the left precordial leads when the electrocardiogram disclosed a transverse electrical axis and in the right precordial leads when the electrical axis was vertical

Certain diagnostic conclusions can be drawn from the ST and T changes in the electrocardiograms of patients receiving digitalis If they are the changes mentioned as being characteristic of digitalis the patient may have a normal or a diseased heart But if distinctly inverted T waves appear during digitalization it is extremely likely that the heart is diseased for the normal heart develops only the ST changes described as characteristic of digitalis Since the ST and T changes which may appear within two to four hours of a large therapeutic dose do not disappear for two to three weeks it is necessary for proper interpretation of the electrocardiogram to determine whether the patient has received digitalis in the preceding three weeks It has been noted (p 51) that repolarization occurs last in the subendocardial myocardium despite the fact that depolarization appears earlier here than in the subpericardial muscle This delayed repolarization accounts for the ventricular gradient which as a rule renders the normal T wave upright otherwise it would be inverted (opposite in direction to the QRS) Digitalis appears to accelerate the repolarization in the subendocardial region reduces or eliminates the differences in duration of repolarization in the myocardium and thereby abolishes or greatly reduces the ventricular gradient The ST-T waves of repolarization become oppositely directed to the QRS and usually negative[345] At the same time this accelerated repolarization shortens electrical systole[346] (QT_c)

Other electrocardiographic changes appear later and usually only after excessive doses of digitalis They are the graphic representation of the disturbances in rhythm and conduction enumerated above as the cardiac symptoms of digitalis overdosage (p 265) These include premature beats especially bigemini excessive slowing of the heart rate prolongation of the P R interval (Fig 58*A*), partial or complete heart block with dropped ventricular beats or atrioventricular dissociation (Fig 58*B*) atrial fibrillation ventricular paroxysmal tachycardia (Fig 58*C*) and inversion flattening or notching of the P wave especially in lead III The P wave changes can usually be eliminated by atropine The duration of electrical systole i e the Q T interval is shortened in comparison with the duration of the entire cardiac cycle R R[20] According to ter Horst[3 8] the *absolute* value of the Q T interval may be shortened lengthened or remain unchanged depending on whether it was originally prolonged of normal length or of less than normal length

DIURETICS

In cases of relatively mild congestive heart failure rest and limitation of salt often result in a satisfactory diuresis with concomitant clinical improvement In others, such an effect is obtained only if digitalis therapy is also employed But many patients with more severe symptoms of congestive heart failure especially with widespread anasarca, respond satisfactorily only if diuretics are utilized in addition to the above measures The fewer the measures required to obtain a good therapeutic result the better in general is the prognosis A variety of diuretics have had their vogue from time to time but the utility of any one of these has been dwarfed by the striking success of the soluble organic mercury salts Since the mercurial diuretics have been used many patients whose outlook for life would not average more than six months to a year have been maintained with various degrees of comfort for many years

MERCURIAL DIURETICS

Mercuhydrin and Other Mercurial Diuretics *Calomel* formerly widely employed as a diuretic often in combination with equal parts of digitalis and squill (1 gram each) as the famous Guy s pill is now rarely used in treating cardiac dropsy because of its limited effectiveness and its toxicity *Merbaphen* (Novasurol), originally used in the treatment of syphilis is an effective diuretic but is rarely used at present because of toxic complications Colitis stomatitis purpura hemoglobinuria hemorrhagic encephalitis and epithelial necrosis of the kidney sometimes with fatal results have been reported These complications are relatively rare with the more recently employed mercurials *Salyrgan* (mersalyl) *mercupurin* or *Mercuzanthin* (mercurophylline) *Mercuhydrin* (meralluride sodium) *Thiomerin* (mercaptomerin sodium) and *Cumertilin* (mercumatilin) The mercurial diuretics now in use usually contain about 5 per cent of theophylline which may add somewhat to the diuretic effect facilitates absorption of the mercurial component and probably reduces local irritation [88]

Thiomerin is one of the newer mercurials with a mercapto or thiol (SH) group in the mercurial molecule obtained by adding thioglycollate instead of theophylline to reduce toxicity Aside from a reported diminution in cardiotoxicity of Thiomerin in animals as compared with other mercurials Thiomerin was found to produce less local irritation and was considered to be suitable for subcutaneous injection Although many observers have reported the use of Thiomerin by subcutaneous injection with relatively few and infrequently severe local reactions [14] Gold and associates[144] reported disturbing local reactions in about 25 per cent of the patients and noted no significant advantage over Mercuhydrin for subcutaneous administration One disadvantage of Thiomerin is its lesser stability than other mercurials when placed in solution

Dicurin procaine (merethoxylline procaine with theophylline) is a new organic mercurial each cubic centimeter containing 0 1 gm of merethoxylline as the procaine salt (equivalent to about 40 mg of mercury) with 5 per cent theophylline added Although Dicurin procaine was recommended to be useful for subcutaneous injection because of minimal local reactions Best et al [27] reported that local reactions including ecchymoses were observed in 20 per cent of patients and following 8 per cent of the injections

Cumertilin (*mercumatilin*) is still another new mercurial diuretic which differs structurally from other mercurial diuretics in that the mercurated methoxypropyl group has no amide linkage and is attached to a ring carbon atom, the ring structure in this compound is a heterocyclic coumarin Like the other currently available mercurials it is prepared in a solution for injection each cubic centimeter containing a concentration of 30 mg mercury and 50 mg of theophylline It is also prepared in tablets for oral administration [285] Preliminary studies indicated Cumertilin is as potent as other mercurial diuretics by injection[279] [4] and that its toxicity and local effect on tissues are likewise similar [24] In a limited experience I have encountered relatively more local painful reactions than with either Mercuhydrin or Thiomerin Data were presented indicating that ammonium chloride is not as essential for a satisfactory diuresis with mercumatilin as with meralluride or other mercurial diuretics [4]

At the present time I most frequently employ Mercuhydrin but have found Thiomerin equally satisfactory except for its lesser stability From the viewpoint of activity Salyrgan Mercuhydrin and Thiomerin have been found equally potent [110] [148] and Citrin and Lyons[80] reported Dicurin procaine to be as potent as Thiomerin

Action of Mercurial Diuretics

The mechanism by which the mercurial salts produce diuresis is uncertain According to the studies of Herrmann and his coworkers [174] the mercurials cause diuresis by liberating ionic mercury which inhibits tubular reabsorption Sollmann and associates[308] found evidence to indicate that they may have an extrarenal action by which they mobilize water and salt from the tissues into the blood stream However the extrarenal theory of mercurial diuresis has been generally rejected on the basis of considerable experimental evidence [158] [7] It is most probable that the mercurial diuretics act directly on the kidneys [158] [7] decreasing the tubular reabsorption of chloride sodium and water [244] In addition they inhibit tubular reabsorption and secretion of potassium [58] [81] There is no significant change in renal blood flow or glomer

ular filtration The striking increase in volume of urinary output after a mercurial diuretic, especially in the patient with heart failure is not due to direct effect on water flow by primary inhibition of tubular reabsorption of water[5] Rather the primary inhibition of chloride and sodium ions secondarily interferes with the passive reabsorption of water in the proximal or distal tubules or the depression of tubular reabsorption of these ions may *increase the urinary load of solutes and* thus impose an osmotic limitation on active tubular reabsorption of water There is evidence that the mercurial diuretics inhibit specifically the reabsorption of chloride ions[236] and that the cations sodium and potassium are carried along with the unresorbed chloride Whereas the concentration of sodium in plasma and therefore in the glomerular filtrate exceeds that of chloride (140 compared with 105 mEq per liter respectively) following a mercurial diuretic the urinary concentration of chloride usually equals or exceeds that of sodium[1,3, 5] However mercurial drugs may have a direct inhibitory effect on tubular reabsorption of sodium as well as chloride[■]

There is a difference of opinion as to whether the site of action of mercurial drugs ■ the proximal or the distal tubule and there is uncertainty as to the mechanism by which tubular inhibition of ionic reabsorption is accomplished The experimental observations of Weston et al [249] Mudge et al [250] and others[273, 43, 243, 180] were interpreted to indicate that mercurials acted on the proximal tubule and this viewpoint appears to be supported by *the finding that in mercurial anuria the* pathologic lesions are essentially in the proximal tubule ■ On the other hand, the ingenious experiments of Duggan and Pitts[95] suggested to them that the mercurial acted on the distal tubule For the fraction of total sodium reabsorption blocked by mercurial action (17 to 21%) coincided closely with the fraction of sodium filtered through the glomerulus which is not reabsorbed by the proximal tubules and is available for distal tubular reabsorption *The theory of distal* tubular action of mercurial is al o supported by the studies of Dale and Sanderson [75] and by the observations that these drugs depress the maximum tubular excretory capacity for Diodrast and PAH [43] which are functions of the distal tubules

More recently histochemical studies likewise suggest ■ distal tubular site of action of mercurial diuretics and also support our present concept of the manner of action of organic mercurial diuretics on tubular function The interference of mercurials with tubular reabsorption of certain ions and water, their depression of tubular excretion of dyes and their inhibition of potassium secretion[21] indicate that the mercurials exert ■ toxic effect on the tubules *which interferes with* fundamental functions The transient and reversible nature of this effect ■ compatible with enzyme inhibition Succinic dehydrogenase an enzyme important in the citric acid (Krebs) cycle, and depending for its activity on the presence of free sulfhydryl (SH) groups, ■ believed to play an important part in the chemical reactions whereby the tubule cells provide the energy necessary for osmotic work required for the active absorption of ions Mercuric salts including mercurial diuretics are capable of inactivating succinic dehydrogenase [161, 8 8] On the other hand BAL which reverses the toxic effects of the poison gas lewisite (an inhibitor of SH enzymes), does so by providing SH groups which compete with the SH enzyme and thus inactivate the lewisite BAL similarly reverses the mercurial inhibition of succinic dehydrogenase[8, 161] and simultaneously diminishes or arrests mercurial diuresis [116] These observations suggest that succinic dehydrogenase is important for tubular reabsorption and that mercurial diuretics inhibit tubular reabsorption of chloride sodium, etc, by combining with the free sulfhydryl groups and thus inhibiting or *inactivating the enzyme succinic dehydrogen*ase [83] In order to localize the site of this inhibition, the blue stain tetrazolium was used as an indicator, acting as a hydrogen acceptor for succinic dehydrogenase and combining with it to form dark blue crystals of formazan, which may be observed microscopically By this method it was noted that succinic dehydrogenase activity ■ greatest in the cells of Henle s loop but more striking was the finding that after administration of a mercurial *diuretic, formazan crystal formation* denoting succinic dehydrogenase activity was minimal or absent in the thick (distal ascending) limb of Henle s loop [251] These findings were interpreted to indicate that mercurial diuretics act on the distal tubules

The pronounced diminution of sodium ex

cretion by the kidney which is characteristic of congestive heart failure ■ reversed by mercurial diuretics Following intravenous injection diuresis begins within one to two hours after administration of the mercurial reaches its peak in four hours and is usually completed in twelve to twenty four hours A daily excretion of 2 to 3 liters is commonplace after a mercurial diuretic and concomitantly there is a weight loss of 3 to 6 pounds Occasionally huge amounts of urine are excreted Careful attention to the weight ■ a useful method of gauging the effectiveness of the diuretic

Indications for Mercurial Diuretics

The mercurial diuretics are indicated in all stages of congestive heart failure but especially when the symptoms fail to respond to rest digitalis and the limitation of sodium salts The most striking benefits are seen in patients with intense anasarca but a sharp diuresis and loss of weight are frequently observed in patients with latent edema Furthermore remarkable benefit may be obtained from the mercurial diuretics in cases of congestive heart failure (pulmonary congestion with or without pulmonary edema) in which failure is limited to the left side of the heart Patients with orthopnea nocturnal dyspnea (cardiac asthma) nocturnal cough due to heart failure or with recurrent attacks of pulmonary edema may be greatly relieved by the administration of the organic mercurials Mercurial dehydration may be indicated as a prophylactic measure against recurrent paroxysmal dyspnea In such patients the administration of mercurial diuretics often serves as a therapeutic test in determining the cardiac or noncardiac origin of protracted cough or dyspnea of uncertain origin

The mercurial diuretics are equally effective in cases of congestive heart failure with atrial fibrillation or with regular rhythm But compared to digitalis effects their action is much more impressive in the latter group in which digitalis often fails to produce a significant diuresis Frequently the mercurial diuretic will evoke a sharp diuresis and loss of edema after rest and digitalization have been given a fair trial without much benefit Cases of congestive heart failure due to coronary atherosclerosis hypertension or rheumatic heart disease respond to the mercurial diuretics with equal effectiveness

Contraindications to Mercurial Diuretics

The chief contraindication to mercurial diuretics is renal impairment But albuminuria or nitrogen retention in the blood does not necessarily forbid the use of these drugs because heart failure itself may produce these abnormalities That they are actually due to heart failure and not to renal insufficiency may be recognized by the dark color of the urine with its richly colored sediment and by the high specific gravity of the urine (1 020 or more) as obtained in a casual specimen or after a concentration test On the other hand if the urine is pale and the specific gravity is 1 014 or less in patients with heart failure it is probable that there is renal insufficiency and mercurials should not be administered This rule is not applicable if the urine is examined when the patient is in the process of active diuresis But although the administration of a mercurial diuretic may be permissible in a patient with heart failure complicated by renal disease further injections are contraindicated if a satisfactory diuretic response is not obtained And indeed in all patients with severe heart failure lack of a significant diuretic effect is a warning against further mercurial diuretics unless some interfering factor ■ altered or adjuvant drugs are used

The mercurial diuretics are contraindicated when heart failure is associated with acute or subacute glomerulonephritis as they may increase the hematuria or cause anuria I have seen both temporary and fatal anuria caused in such cases by the use of Salyrgan or mercupurin However further study of the possible usefulness of mercurial diuretics in renal edema is needed One of the major risks of the use of mercurial diuretics in glomerulonephritis is the danger of mercurial retention if a diuresis is not obtained and especially if there is severe oliguria However mercurial drugs frequently produce an excellent diuresis in patients with chronic glomerulonephritis with edema The mercurial diuretics should be used with caution and in relatively small doses in elderly patients who are likely to have urologic diseases Tscherning[318] has reported the occurrence of acute retention in old men with large prostate glands which was attributed to a profuse Salyrgan diuresis I have observed this many times Hines[161] reported a high incidence of uremia in a series of

patients with hypertensive and coronary heart disease and congestive heart failure

Mercurial diuretics irritate the colon and are therefore contraindicated in the presence of *inflammatory lesions of the large bowel* For the same reason it is advisable not to administer purgatives acting on the colon on days when Salyrgan or mercupurin is administered The mercurial diuretics are contraindicated in persons with a hypersensitivity to the mercury ion and Dicurin procaine should not be given to persons sensitive to procaine

Toxic and Other Undesirable Effects of Mercurial Diuretics

The toxic and undesirable effects of mercurial diuretics may be considered under five headings

1 Immediate reactions
2 Mercurialism
3 Local irritation
4 Digitalis toxicity
5 Electrolyte disturbances

1 Immediate Reactions A number of serious and even fatal reactions have been reported immediately after injection of mercurial diuretics, even in patients who had had many previous injections of the same drug[351] These are rare with the first injection and when mild reactions occur subsequently they tend to become more severe with repeated administration Chills, fever[339] nausea and vomiting and cutaneous rash, occurring on the day of injection have been attributed to drug idiosyncrasy Sometimes these are warning reactions more severe manifestations occurring with continued exhibition of the mercurials[46] Among the immediate reactions to the injection of mercurial diuretics are transient dizziness, weakness pallor, perspiration substernal oppression, dyspnea or asthmatic attacks and changes in cardiac rhythm They occur very rarely In some instances collapse and sudden death have followed an injection of a mercurial diuretic[45] The cause of these reactions is uncertain[351] Ben Asher[18] believed that he prevented a recurrence of reaction by injecting the mercurial very slowly or giving it after an intravenous infusion of sodium thiosulfate or by injecting it intramuscularly Sometimes a change to another mercurial eliminates further untoward reactions In these circumstances sensitivity is not related to the mercury ion but to the given organic compound

2 Mercurialism Manifestations of mercurial poisoning are relatively rare with the organic mercurial preparations now in use Safety is provided by the excretion of 70 to 85 per cent of the mercurial in 24 hours if there is a diuresis of at least 2000 cc[194] Stomatitis with excessive salivation, dermatitis, colitis with diarrhea which may be hemorrhagic, and renal disturbances (hematuria, anuria and renal insufficiency) have been reported on occasion If mercurial toxicity is recognized early treatment with BAL should be instituted (initial dose 5 mg / kg) or about 3 cc of a 10 per cent solution of BAL in benzyl benzoate and peanut oil intramuscularly followed by 1 5 to 2 5 mg /kg (usually 1–1 5 cc) every four hours thereafter for at least three days

3 Local irritation is an annoying characteristic of the mercurial diuretics Imperfect intravenous injections cause a severe periphlebitis with pain and disability lasting several days, and occasionally followed by tissue necrosis, but such local tissue reactions are much less common with mercuhydrin and Thiomerin than with Salyrgan theophyllin or Mercuzanthin It is essential that the needle be properly placed within a vein before the drug is injected and repeated aspiration of blood should be performed to be certain the needle has not slipped

4 Digitalis Toxicity and Redigitalization Another reported complication of rapid diuresis with mercurials is the mobilization of digitalis from edema fluid and serous effusions[90] It was reported that some of the digitalis is retained in the edema fluid[4] In the course of active diuresis the digitalis containing extracellular fluid has been presumed to reenter the bloodstream and to cause redigitalization or excessive digitalization of the patient with consequent ventricular slowing arrhythmias vomiting and mental confusion This theory is improbable because quantitative studies disclosed minimal or no digitalis in the edema fluid of digitalized patients[315] It is highly probable that mercurial diuresis predisposes to and precipitates digitalis toxicity by depleting body potassium A direct myocardial toxic effect has been predicated to account for cardiac arrhythmias induced following mercurial diuresis But the "myocardial effect may represent potassium depletion

According to Macht[274] injection of mer

curial diuretics reduced the clotting time of the blood of rabbits and cats Marvel and Shullenberger [8] reported thromboembolic phenomena associated with rapid diuresis in the treatment of congestive heart failure They recommended the use of prophylactic anticoagulant therapy

Despite the occasional toxic effects of mercurial diuretics these drugs are rarely dangerous if used with discretion and with regard to the above contraindications There are many patients now who have received many hundreds of injections of mercurial diuretic without apparent harm Fineberg[124] has reported a case in which 343 injections of Salyrgan and mercupurin were given without deleterious effect over a period of seven and one half years Friedenson[135] reported a similar case in which 627 injections were administered over a period of twelve years I have given one patient with heart failure due to rheumatic heart disease more than 700 intravenous injections of mercurial diuretics, and many others have received approximately one injection weekly for more than five years Tarr and Jacobson[3,6] in a study of 30 necropsies on subjects who had received Salyrgan for a long time found indications of renal damage caused by the mercurial in only one case

5 Disturbances in Blood Electrolyte Pattern

Effects of Excessive Mercurial Diuresis Enthusiasm for the mercurial diuretics especially in combination with low sodium diets was soon followed by observations of unpleasant and sometimes serious clinical manifestations attributed to excessive and too rapid diuresis Muscular fatigue muscle cramps weakness and occasional prostration or collapse were attributed to dehydration and especially to loss of electrolytes particularly sodium Psychotic disturbances (drowsiness, mental confusion delirium) often attributed to digitalis toxicity, may also be due to overenthusiastic use of the mercurials Some of the cases of so called cardiac cachexia may be due in part at least to mercurial diuretics Poll and Stern [64] reported seven such cases with three deaths due to rigid mercurial diuresis After a period of preliminary weakness intense anorexia and mental apathy the patients suffered from restlessness, mental confusion and rarely hallucinations and delirium Progressive coma and death ensued in some cases Following vigorous desalting with mercurials fixation of the specific gravity of the urine at 1 010 and azotemia may persist for several weeks Black and Litchfield reported eight cases of uremia five of them fatal among 62 patients with heart failure treated with low salt intake and mercurial diuretics [2] Cerebral thrombosis with hemiplegia has been attributed to profound diuresis and the fall in blood pressure engendered by the injection of mercurial diuretics in full therapeutic doses [2,3] Occasionally profuse diuresis was held accountable for a loss of calcium sufficient to produce tetany in predisposed individuals [6] Other metabolic disturbances associated with intense diuresis have been postulated to account for the instances in which an attack of gout was precipitated in gouty persons [248]

In recent years distinctive disturbances in blood electrolyte pattern have been recognized in patients in heart failure who are being treated with mercurial diuretics alone or in combination with adjuvant diuretics low sodium diets and by cationic resins (Fig 61) Clinical syndromes characterized by many of the features listed above and others have been attributed to these chemical disturbances involving electrolytes and other blood constituents These will be individually considered

Hyponatremia the Low Sodium Syndrome [29, 210, 61, 224, 208] In certain patients with congestive heart failure the blood electrolyte pattern is characterized by a striking reduction in the concentration of plasma sodium (hyponatremia) to levels of 130 to 110 mEq /L or occasionally lower Correspondingly there is a diminished concentration of anions involving both chloride and bicarbonate There is a mild to moderate acidosis and often variable azotemia These chemical changes have been associated with a clinical picture which has been variously termed the salt depletion syndrome or ' the low sodium syndrome ' The implication is that depletion of the body salt or the low plasma sodium concentration and associated electrolyte disturbance are responsible for the clinical syndrome

Mechanism and Types of Hyponatremia There is considerable confusion in clinical practice with respect to the mechanism responsible for the clinical picture and electrolyte disturbance and with respect to the rela

tionship of the clinical picture to the blood electrolyte disturbance A low sodium concentration in the plasma (below 130 mEq/L) is seen in conditions with malnutrition such as chronic tuberculosis and in a variety of other chronic conditions, without any clinical manifestations of the so-called low sodium syndrome and in fact without any symptoms at all due to the low sodium[8,9] The hypo-osmolarity in this chronic asymptomatic form of hyponatremia may be due to nutritional disturbances affecting primarily cellular electrolyte concentration The plasma (and extracellular) low sodium concentration may represent a secondary adjustment whereby sodium metabolism is regulated around this new low level The total store of extracellular sodium as well as extracellular sodium concentration, is low[77] This group of cases is significant in two respects First it indicates that clinical manifestations do not necessarily result from hyponatremia Second in at least some cases of heart failure, chronic malnutrition may be entirely or partly responsible for hyponatremia and none of the clinical manifestations can be properly attributed to this chemical change

In a second group of cases the low sodium electrolyte pattern can be truly attributed to *sodium depletion* Sodium depletion is observed in surgical patients whose sole intake consists of parenteral fluid containing no sodium, in patients with fistulas or drains causing large daily losses of intestinal, biliary or pancreatic fluids, in patients with severe protracted vomiting or diarrhea without concomitant sodium replacement, in Addison's disease and sodium losing nephritis, and in subjects with intense sweating in a hot environment Sodium depletion occurs in congestive heart failure when there is a combination of low sodium intake with excessive sodium loss Low sodium intake may be due to anorexia or extremely restricted sodium intake, the increased output may be due to profuse diuresis induced by mercurial diuretics to paracentesis of ascitic fluid to thoracentesis, to diarrhea and to excessive

ELECTROLYTE PATTERNS CONGESTIVE HEART FAILURE

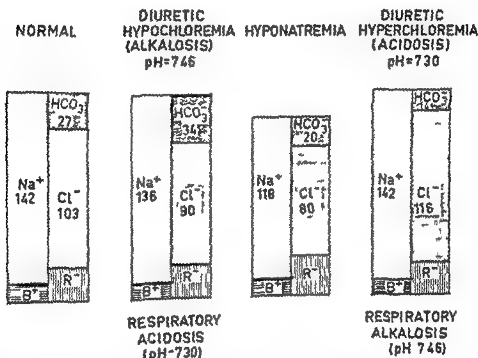


Fig 61 Gamble-type diagram Left-hand columns represent concentrations of chief plasma cations right hand columns the chief plasma anions Total concentrations equal in each pair denoting electrochemical neutrality B^+ denotes positive ions other than sodium viz K^+ Ca^{++} Mg^{++} etc R^- denotes negative ions other than chloride and bicarbonate viz sulfate phosphate protein

sweating in hot weather. The onset of the clinical and chemical features of sodium depletion may occur rather acutely after the diuresis or after the pleural or abdominal tap.[144] In this group dilution occurs due to greater loss of sodium than of water, but external loss of sodium is the primary factor.

In a third group of cases, often erroneously included under the category of sodium depletion, a sharply reduced sodium intake is an important causative factor but there is no evidence of abnormal sodium loss. Whatever the contributory role of mercurial diuretics, they do not act by causing a profuse diuresis and sodium depletion. On the contrary, the mercurials may be ineffective in producing diuresis and commonly there is oliguria; the sodium concentration of the urine is extremely low or sodium may be virtually absent. At the same time that the sodium intake is extremely low, the intake of fluids is unrestricted and there may be a positive water balance in view of the common oliguria. Thus the hyponatremia in these cases without sodium depletion is attributed to *water dilution of the extracellular sodium*. It is possible that a shift of extracellular sodium into bone or cells[24] also contributes to the hyponatremia. Occasionally *dilution hyponatremia* may be acutely complicated by sodium depletion due to isolated or repeated thoracentesis or abdominal paracentesis. In this type of dilution hyponatremia, associated with severe cardiac or renal insufficiency or cirrhosis of the liver, the total store of extracellular sodium is increased despite the low sodium concentration.

The mechanism of the dilution type of hyponatremia is obscure because the dilution explanation does not provide the reason for its occurrence in some patients with congestive heart failure but not in others receiving essentially the same dietary intake of sodium and similar diuretic therapy. Although there is no general agreement on this point, underlying renal impairment appears to be a common and important, if not essential, underlying factor responsible for the development of the dilution type of hyponatremia.[illegible] It is not clear whether the low sodium intake and the mercurial diuretics in combination cause further renal damage to a predisposed kidney and thereby then induce hyponatremia, or whether the kidney function is already sufficiently impaired and the low sodium mercurial combination merely prevents restoration of isotonicity of extracellular fluids by sodium while water is being retained by the malfunctioning kidney. It is of interest that the dilution type of hyponatremia is particularly likely to occur in the elderly patient with cardiac failure, since the elderly patient usually has a low reserve kidney.

Although water excretion by the kidney in heart failure is generally regarded as normal except insofar as water is retained secondary to sodium, there is evidence that, especially in advanced stages of heart failure, a water load is poorly excreted. Whereas the restricted sodium intake tends to balance the minimal sodium excretion, there is usually no restriction of fluid intake to balance the impaired water excretion. The retained water then dilutes the extracellular sodium and induces hyponatremia. This type of dilution hyponatremia due primarily to water retention while the external balance of sodium is unchanged resembles somewhat the clinical situation in water intoxication.[44] The impairment of water diuresis may be due to increased secretion of the antidiuretic hormone (ADH) in advanced refractory heart failure rather than to renal impairment, as suggested by the similarity of the clinical picture induced by administration of pitressin tannate in oil in patients with heart failure[150] on a liberal water but very restricted sodium intake.

Another factor in these cases of dilution hyponatremia is the state of the circulation, more specifically the advanced stage of congestive heart failure. The refractoriness of the heart failure is a characteristic feature and is commonly attributed to the electrolyte disturbance. Often, however, the sequence of events indicates that the unresponsiveness to therapy, especially to mercurial diuretics, as well as the abnormal electrolyte pattern is secondary to more fundamental widespread cellular disturbances which are primarily due to the advanced and virtually irreversible stage of failure of the heart and circulation.

Clinical Features. The clinical features listed as part of the low sodium syndrome include (1) gastrointestinal symptoms—anorexia, nausea, vomiting; (2) neurologic symptoms—apathy, drowsiness, restlessness, con

fusion, convulsions, coma, (3) muscular—weakness, cramps, (4) circulatory—tachycardia, shock, (5) laboratory findings including hyponatremia, hypochloremia, acidosis, rising blood urea, oliguria, low urine sodium chloride. Although thirst is commonly mentioned as one of the symptoms, it is almost always absent. Thirst occurs with dehydration, not with the low sodium syndrome. The symptoms of hyponatremia due to sodium depletion differ somewhat from those attributed to dilution hyponatremia. Weakness or prostration and muscle cramps are fairly common after excessive mercurial diuresis, presumably due to sodium depletion. With more intense diuresis, and especially after removal of pleural and ascitic fluid, the clinical picture of shock may develop in association with evidence of uremia. On the other hand the clinical picture associated with the dilution type of hyponatremia often develops more insidiously. Anorexia and apathy are early symptoms. There is a poor diuretic response to mercurial diuretics. Nausea and vomiting occur and the patient is drowsy much of the day. There is progressive oliguria and azotemia while edema persists or increases despite treatment. Severe mental symptoms with psychosis, confusion, coma and death may occur. There is increasing uremia in advanced stages of the syndrome.

It is apparent that many of the clinical features attributed to the so called low sodium syndrome are non specific and could be due to other disturbances or complications frequently observed in congestive heart failure. There is often great uncertainty as to whether the symptoms attributed to hyponatremia in heart failure are not actually due to concomitant pulmonary embolism, digitalis intoxication, primary renal disease, acute myocardial infarction, internal bleeding from anticoagulants, intercurrent infection or intractable and often irreversible heart failure.

Treatment When hyponatremia is due to sodium depletion, treatment consists in increasing sodium intake by mouth in mild cases, or administering hypertonic sodium chloride (300 cc of a 3% or 5% solution) intravenously, when the need is more urgent or the patient is unable to take the sodium orally. In the presence of significant acidosis 5 per cent sodium bicarbonate or 1/6 molar sodium lactate may be administered. Vigorous efforts to raise the sodium concentration to normal involve risk of increasing anasarca and acute pulmonary edema. The isolated occurrence of muscle cramps following a mercurial diuretic can usually be prevented by the administration of 0.3 gm of quinine on the day of the injection.

When hyponatremia is of the dilution type one should consider carefully other possible causes for the clinical picture than hyponatremia, even when the latter is present. Overdigitalization should be corrected and a careful survey made as discussed under the management of intractable heart failure. In these cases it is my present policy to restrict fluid (as well as sodium) almost as stringently as in cases of acute oliguria due to toxic nephrosis (lower nephron nephrosis). The administration of sodium orally or intravenously is contraindicated. Although the concentration of plasma sodium may be elevated and the abnormal electrolyte pattern restored toward normal by this means, and although there is rarely an equivocal clinical improvement, the latter is temporary and does not alter the usually fatal clinical course.[334] Recently Laragh[96] reported small to striking increases in serum sodium concentration when potassium chloride (4–22 gm daily of a 20% solution) was administered orally to patients in heart failure with hyponatremia. Despite the rise in sodium concentration there was no significant diuresis. It was postulated that serum sodium concentration was elevated by a release of sodium from the cells in exchange for potassium. The danger of hyperkalemia should be considered because of the inability of many cardiac patients to metabolize or excrete potassium normally.

Diuresis Hypochloremia with Alkalosis and Hypokalemia[296, 310, 312, 294] Repeated mercurial diuresis may cause three types of response with respect to blood electrolytes. (1) Mercurial diuresis and associated body adjustments usually result in no significant disproportion between loss of sodium and loss of water. Disproportionate chloride loss is promptly adjusted. In such cases of heart failure there is no important change in blood electrolyte pattern due to the mercurials. (2) Occasionally, mercurial diuresis in conjunction with low sodium intake and other factors which are incompletely understood may cause a loss of sodium disproportionate to

the loss of water or it may cause renal impairment of response to normal water intake In either circumstance hyponatremia results (3) The third and most characteristic response to mercurial diuretics is an excretion of chloride in excess of sodium relative to their concentrations in the plasma The excess of chloride is excreted with potassium ammonium or both When mercurial diuretics are repeated frequently and the diuresis is profuse striking changes in blood electrolytes may occur These consist of a marked reduction in plasma chloride (below 90 mEq per liter) with little or no reduction in plasma sodium an increase in plasma bicarbonate and in pH (alkalosis) A reduction in plasma potassium may result from the additional excretion with chloride The total pattern is described as hypochloremic alkalosis with hypokalemia In some cases of pulmonary disease with carbon dioxide retention (respiratory acidosis) there is a similar pattern with regard to elevation of bicarbonate and reduction of plasma chloride concentration This pattern may be distinguished by the low pH and clinically by the history of pulmonary disease as contrasted with the history of profuse and frequent diuresis following the injection of mercurials Diuresis hypochloremia following mercurials resembles the electrolyte pattern observed as a result of vomiting (of hydrochloric acid in gastric contents) in cases of pyloric stenosis or other conditions with profound or prolonged emesis Hypochloremic alkalosis in heart failure is most likely to follow mercurial diuresis if anorexia prevents replacement of excreted chloride and especially if there is associated vomiting e g due to digitalis toxicity On the other hand if ammonium chloride is administered in conjunction with mercurial diuretics excessive chloride loss may be replaced and hypochloremia avoided

The hypochloremic alkalosis due to mercurial diuresis may be significant clinically in two respects (1) It often interferes with further diuresis in fact mercurial unresponsiveness should suggest hypochloremia as one of the possible causes Diuresis probably depends on a specific inhibitory effect of the mercurial on the tubular reabsorption of chloride an effect which may be minimal when plasma chloride falls to low levels and when there is a markedly decreased quantity of chloride filtered by the glomeruli (2) If hypochloremic alkalosis is severe it may be responsible for clinical symptoms characterized by refractory heart failure apathy anorexia weakness drowsiness mental confusion and uremia The clinical features other than the chemical findings resemble those associated with hyponatremia

Diuresis hypochloremia with alkalosis may be corrected by the administration of chloride ion in acidifying agents such as hydrochloric acid or ammonium chloride The ammonium ion is metabolized and the free chloride ion has the same effect as hydrochloric acid If the patient can take oral medication he is given 6 to 9 gm of ammonium chloride daily in tablet form If he is intolerant to this or if urgent treatment is indicated ammonium chloride is administrated intravenously in a 1 per cent solution in 5 per cent glucose in water Because of the toxicity of the ammonium ion in high concentration (convulsions shock and death) the ammonium chloride must be given slowly not exceeding 100 cc per hour and not more than 1500 cc daily Potassium may have to be added if there is a significant hypokalemia There is evidence that when potassium salts are administered to patients with hypochloremic alkalosis calcium should also be given to avoid tetany [106]

Potassium Depletion The potassium depletion which may be caused by mercurial diuresis may be enhanced also by the use of other agents employed in the therapy of heart failure Continuous ammonium chloride therapy increases potassium excretion in combination with the additional chloride ions The tendency of cationic exchange resins to cause potassium depletion by binding potassium and increasing its fecal excretion has been discussed When Diamox is used as a diuretic alone or in combination with mercurials potassium excretion is increased along with the increase in bicarbonate excretion All these factors are rarely responsible for clinical symptoms unless the intake of potassium is poor In digitalized patients mercurial diuretics may be responsible for digitalis toxicity, especially disturbances in rhythm presumably because the mercurials cause potassium depletion (p 274) Treatment of potassium depletion consists of the administration of 2 gm of potassium chloride three times daily

orally or 3 gm of potassium chloride (40 mEq) in 1000 cc of 5 per cent glucose in water intravenously

Hyperchloremic Acidosis Other electrolyte disturbances may occur in patients receiving mercurial diuretics due not to the mercurials but to other diuretics or to resins which are being used simultaneously Thus hyperchloremia with acidosis (p 284) may occur as a result of ammonium chloride or resin therapy or as a consequence of the carbonic anhydrase inhibitor Diamox The e disturbances may modify the electrolyte changes due to the mercurials

The Administration and Dosage of Mercurial Diuretics

The soluble organic mercurial diuretics may be administered intravenously intramuscularly subcutaneously orally, by rectal suppo itories or intraperitoneally Mercuhydrin Thiomerin Mercuzanthin (mercurophylline) and Salyrgan theophylline are those in common u e They are equally effective as diuretics but it appears that Mercuhydrin and Thiomerin are least apt to cause local irritation after intramuscular injection The mercurials should be administered in the morning if possible in order that most of the diuresis is completed before the patient retires for the night

Usually I begin with an intramuscular (gluteal) injection of 0 5 cc (8 minims) to test the patient s sensitivity If this causes headache fever gastric disturbances or a rash I change to another mercurial which may be better tolerated If there are no untoward symptoms after this preliminary injection and no significant diuresis results I administer 1 cc (15 minims) of the medicament in 24 to 48 hours depending on the urgency of the ca e This dose is usually adequate for continued diuretic action and should be repeated according to need Two cubic centimeter do es produce a more profuse diuresis and may be preferable but the increa e in urinary output is le s per cc of the drug [44] On rare occasions 3 to 4 cc doses may be effective when the smaller doses have failed After the first test do ■ intramuscularly, I may administer the injection intravenously or intramuscularly depending on the degree of irritation cau ed by the latter and the ease of intravenous administration The importance of careful intravenous injections and avoidance of infiltrating the perivenous tissue has b noted All intravenous injections must given *slowly*

A nonedematous area should be chosen intramuscular injection so as to permit a sorption Usually the injection is given in t upper and outer quadrant of the buttoc When the patient is obese the needle shou be of sufficient length to reach the muscul tissue Sometimes the injections cause painfu nodular infiltrations For this reason it may l desirable to add 1 cc of 1 per cent procaine t the mercurial solution before injecting it int the muscle or Dicurin procaine may be trie If intramuscular injections are ineffective, i is always wise to switch to the intravenou route Following such a change in procedure, have several times observed an effective di uresis after the intramuscular injection ha been impotent

Because it appears that Thiomerin Mercuhydrin and perhaps other mercurials may be given subcutaneously with relatively little pain or other reaction, it has been recommended that cardiac patients be taught to give their own injections just as diabetics self administer insulin [301] However, this may be permissible only if one is certain that a given patient s state of heart failure is quite stabilized The need for careful observation of the patient in heart failure who requires mercurial injections is such as to preclude self administration in most cases

Frequency of Injections The frequency of mercurial injections depends on the clinical course and the patient's response A thorough elimination of all edema fluid, obvious and latent in the pulmonary as well as systemic tissues is the desired objective A daily record of the patient s weight, carefully determined is the most useful guide to control of his retention of fluid A record of intake and output of fluids may al o be useful but only if these are carefully ob erved Gold[143] recommends the administration of a daily mercurial diuretic in combination with other therapeutic measures until the patient's "dry" or basal weight is obtained (This is rarely necessary and may be hazardous) Thereafter the injections are spaced at intervals which will prevent fluid retention Obviously, the more rigid the limitation of sodium intake the less often or the less likely the need for the diuretic In practice mer

curial diuretics are administered between twice weekly and once in two weeks However, the frequency of injections should be individualized for each patient as determined by symptomatology and clinical examination as well as weight It is rarely desirable to *cause daily weight losses exceeding 2 to 3 pounds* if symptoms of dehydration and prostration are to be avoided

Mercury Fastness. Enhancement of Mercurial Diuresis Patients in heart failure sooner or later become unresponsive to mercurial diuretics This state has been termed "mercury fastness" Usually this is observed in the end stages of failure and after numerous injections of mercurials This unresponsiveness has been attributed to low glomerular filtration and the consequent small quantity of sodium reaching the tubules [344, 85] Thus this small quantity of filtered sodium can be completely or almost completely resorbed despite the action of the mercurial The administration of sodium might restore a mercurial diuresis but more sodium will be retained than is excreted Mercury fastness has also been ascribed to chloride depletion caused by preceding mercurial injections If the mercurial is regarded as causing diuresis by *inhibiting tubular reabsorption* of the chloride ion then chloride depletion by mercurials and diminished glomerular filtration of chlorides may result in almost complete tubular reabsorption of chloride despite the mercurial However neither explanation accounts for all the features of mercury fastness Adrenocortical activity may also contribute to mercury fastness by enhancing tubular reabsorption of sodium [347] It is probable that more fundamental processes associated with advanced heart failure are responsible for the unyielding sodium and water retention All the factors which may contribute to refractory heart failure *may be concerned also in mercury fastness* including pulmonary infection or embolism under or overdigitalization disturbances in electrolytes and so forth The simultaneous exhibition of drugs with antidiuretic effect may impair the response to mercurials e g morphine Demerol and related drugs [1] barbiturates, pitressin and adrenocortical and other sodium retaining hormones

A variety of agents have been employed to enhance the diuretic response to mercurials Ammonium chloride (p 284) is employed most commonly A common procedure is to administer 2 to 3 gm in tablet form, orally, three or four times daily, for two days prior to the injection of a mercurial Aminophylline may be administered intravenously (0 25–0 5 gm) *one or two hours after the mercurial is injected* or 0 5 gm may be mixed with the mercurial [35] This may be given in addition to ammonium chloride preceding the mercurial Decholin (sodium dehydrocholate) ascorbic acid and more recently pyridoxine [347] (100 mg) have been administered intravenously together with the mercurial in order to potentiate the effect of mercurial diuretics Occasionally Diamox (p 282) has been effective in activating mercurial diuresis after the patient appeared refractory In most patients with heart failure who require mercurial diuretics I have found no need for ammonium chloride or other potentiating adjuvants If diuresis is satisfactory with a dose of 2 cc of the mercurial but clinical progress appears inadequate I increase the frequency of injections rather than the dose of the mercurial and rather than adding diuretic adjuvants At the same time of course the *proper administration of all other therapeutic agents* is essential All the adjuvants are tried only if there is no definite diuretic response to the mercurials Ammonium chloride is also given if frequent mercurial diuresis is responsible for chloride depletion and hypochloremic alkalosis

ORAL DIURETICS MERCURIALS AND CARBONIC ANHYDRASE INHIBITORS

It would be highly desirable to obtain a diuretic agent which could be given orally and yet act as effectively as parenterally administered mercurial diuretics without producing significant toxic manifestations No available *oral diuretic* satisfies this objective When the cardiac patient appears to become refractory to parenterally administered mercurials there is often a desperate trial to substitute other diuretics in the hope of greater effectiveness this is virtually futile On the other hand if the advantage of *oral* versus *parenteral administration* is the chief objective and if some sacrifice of potency and speed of action is permissible then oral diuretics now available may be employed with gratifying therapeutic effectiveness in many patients with congestive

heart failure. When effective, such oral diuretics offer the advantages of continuous instead of intermittent diuresis, avoidance of injections or diminution of their frequency, and reduction in the number of visits to the physician by ambulant patients who do not otherwise require such continuous clinical observation.

Oral preparations of Salyrgan-theophylline, mercuzanthin and Mercuhydrin, also in combination with ascorbic acid,[39] have been long available in tablets containing about 30 mg of mercury or slightly less than the amount in 1 cc of the parenteral preparation. Various dosage schedules have been employed, such as two or three tablets each morning after breakfast, one tablet three times daily, or five tablets in a single dose every few days. Although these preparations have produced a satisfactory diuretic response in many patients,[40] they have not gained any significantly widespread acceptance in clinical practice because of inadequacy or uncertainty of diuretic effect and a relatively high incidence of toxic manifestations. The latter include, most commonly, abdominal cramps with or without diarrhea, nausea, painful gums or albuminuria and other evidences of mercurialism.[88] For this reason adequate frequent supervision by a physician is necessary.

Neohydrin. Efforts have continued to produce more effective oral mercurial diuretics with greater potency relative to toxicity.[155, 19] Currently the most promising is *Neohydrin* (chlormerodrin) (3-chloromercuri-2-methoxypropylurea), which is available in tablets containing 10 mg of mercury, compared with 30 mg in most of the other oral mercurial tablets. It is claimed that Neohydrin has three to five times the potency of oral Mercuhydrin[155] and hence the lower mercury content needed per tablet of Neohydrin. Various observers have reported that Neohydrin produces a satisfactory natriuresis and diuresis almost comparable to that of a mercurial administered parenterally in about two thirds or three quarters of patients with congestive heart failure,[114] and further that 50 to 90 per cent of cardiac patients can be treated as well with Neohydrin as with parenteral mercurials.[45, 4, 189, 90] Administration is begun with one to three tablets given in a single dose in the morning or in divided doses. The dosage is gradually increased over a period of weeks, as required to obtain a satisfactory diuresis without unpleasant or toxic reactions. Frequently the effective dosage is five to eight tablets daily (equivalent to 1 to 2 cc Mercuhydrin by injection twice a week), but the higher and more effective doses are accompanied by the highest incidence of side actions. Some patients report a satisfactory result with one or two tablets daily. In such cases it is desirable to review critically the need for any diuretic. However, after a satisfactory control of heart failure is attained, a lower maintenance dose may be more effective then the dose needed to achieve initial control. Toxic reactions, usually nausea or other gastrointestinal disturbancs, are encountered in 15 to 25 per cent of cases, but discontinuation of the drug because of these side actions is necessary in only about 10 per cent of the cases. In general, it appears that Neohydrin is more effective and produces significantly fewer reactions than any of the previously available oral mercurial diuretics.

Nevertheless, nothing in this section should be construed to indicate any enthusiasm on my part for Neohydrin or indeed any currently available oral diuretic. None of them are in a class with the parenterally administered mercurial diuretic. Almost always in clinical practice I either administer a mercurial diuretic parenterally or find no need for any diuretic. In ambulant patients with mild congestive heart failure receiving weekly injections of mercurials, Neohydrin may serve to diminish the frequency of injections or entirely obviate their use. But in many, if not most, such cases it will be found that the injections can be diminished in frequency or eliminated without the substitution of Neohydrin, especially if careful attention is paid to other therapeutic measures.

Diamox. Interest has centered on a group of non-mercurial compounds, the carbonic anhydrase inhibitors, which act as diuretics by inhibiting the tubular reabsorption of sodium and water, but by a different mechanism from that involved in mercurial diuresis. *Diamox* (acetazoleamide) (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide), one of the most potent carbonic anhydrase inhibitors and of remarkable low toxicity, causes a significant diuresis of sodium, potassium, bicarbonate and water when administered intravenously[134] or orally.[134] There is little effect on chloride or phosphate excretion, but urinary excretion of titratable acidity and am

monia is abolished and the urine is rendered alkaline.[133] Diuresis begins about an hour after oral administration of Diamox, reaches a peak in two hours and is completed within five to eight hours. If the drug is repeated at eight hour intervals, the diuretic effect diminishes progressively, and if continued each day it becomes virtually ineffective after three days, possibly because of the development of acidosis and more particularly a low plasma carbon dioxide tension.[133, 134, 233] The ingestion of Diamox greatly increases the rate of maximal water diuresis.[144, 75]

It is generally accepted that the conservation of sodium and development of an acid urine is dependent on the activity in the tubule cells of the enzyme carbonic anhydrase. This promotes the formation of carbonic acid from water and carbon dioxide, whereupon the carbonic acid dissociates and releases H^+ which is secreted into the tubule lumen in exchange for sodium ion.[1, 2] By inhibition of the activity of carbonic anhydrase and thereby the formation of carbonic acid, hydrogen secretion is greatly diminished and sodium reabsorption reduced. Since K^+ and H^+ compete for the tubular mechanism by which these ions are secreted, reduction in H^+ secretion increases K^+ secretion.[23] The increased Na^+ and K^+ excretion also results in a diuresis of water. These cations are excreted chiefly with bicarbonate because the absence of H^+ abolishes the normal conversion of bicarbonate ions to carbonic acid, which is reabsorbed as carbon dioxide.

Diamox is now available as a 250 mg. tablet for oral use. Its dose is about 5 mg. per kilogram body weight, but usually one or occasionally two tablets are effective. A single dose is administered daily in the morning and the diuresis is completed within eight hours. Responsiveness is usually reestablished by the next day. To avoid refractoriness I have frequently prescribed Diamox once daily for three days and omission on the fourth day, or once daily and omission on the sixth and seventh days. Side actions have occurred very infrequently and have rarely necessitated discontinuation of the drug. Drowsiness, lassitude and paresthesias were noted occasionally but disappeared when the drug was discontinued. Blood electrolyte changes which may be induced are hyperchloremic acidosis and hypokalemia, but these are mild with therapeutic dosage.[134] The reduction in plasma bicarbonate inhibits further diuretic activity of the Diamox.

The chief value of Diamox has been found in ambulant patients receiving regular injections of a mercurial diuretic.[134, 17, 209] In such patients the frequency of injections may be diminished, and in about 80 per cent the injections may be discontinued for relatively long periods by substituting oral Diamox. Diamox is more effective in substituting for maintenance injections of mercurials than in initiating control of a severely edematous cardiac patient. Many of the comments made regarding Neohydrin apply to Diamox. Diamox possesses the advantage of less side action or toxicity. Disappointment with Diamox is sure to follow the hope that it is as effective or even almost as effective as an injected mercurial diuretic in patients with severe congestive heart failure, or the expectation of a striking copious diuresis such as one often encounters with the mercurial. The physician is especially likely to find the drug unsatisfactory if he resorts to Diamox only in cases of intractable heart failure after the patient has become refractory to parenteral mercurials. On the other hand, Diamox may be extremely helpful in some cases of intractable heart failure, not as the sole diuretic but in restoring or increasing responsiveness to a mercurial diuretic. Rubin and associates[182] described a striking restoration of responsiveness to mercurial diuretics following the production and maintenance of hyperchloremic acidosis by Diamox and ammonium chloride. Five hundred mg. of Diamox may be given daily for five days. On the fourth and fifth days 10 gm. of ammonium chloride is administered orally in divided doses and continued on the sixth day without Diamox. On the seventh day and, if necessary, for several days thereafter, a mercurial diuretic is administered intramuscularly while ammonium chloride therapy is continued. The hyperchloremia induced by Diamox and ammonium chloride accounts for the restoration of mercurial effectiveness, since the primary action of the mercurial may be on the reabsorption of the chloride ion; elevation of plasma chloride concentration may enhance mercurial diuresis, especially if the plasma chloride concentration was previously diminished by mercurial diuresis or other factors. However, when Diamox is used as a diuretic rather than as a mercurial potentiator, am-

monium chloride should not be administered as the resulting acidosis inhibits Diamox activity Diamox may also prove of special value in the cases of heart failure secondary to obstructive emphysema with cor pulmonale in which there is a retention of carbon dioxide [53, 9] but there is disagreement as to the efficacy of Diamox in such cases [71]

ACIDIFYING SALTS

Ammonium chloride, ammonium nitrate and calcium chloride have been regarded as diuretics which act by causing acidosis [137] In my experience these substances, when employed alone are of no practical value as diuretics in the treatment of heart failure I have employed ammonium chloride only as an adjuvant preliminary to the administration of mercurial diuretics and then only infrequently There is evidence that the potentiation of mercurial diuresis by ammonium chloride[186] is not due or not entirely due to the production of acidosis [200] Hilton[180] observed that the potentiating diuretic effect of ammonium chloride on a mercurial in normal subjects was independent of the presence of acidosis or of its intensity The potentiating effect of ammonium chloride on mercurials has been attributed to the chloride ion rather than to its acidotic effect The ammonium ion is metabolized by the liver while the excess chloride or nitrate then carries sodium with it and consequently a corresponding quantity of fluid is excreted Ammonia production through ammonium producing enzymes such as glutaminase, is a regulatory response to ingested acid substances but lags the first two days During this initial period acidic salts are most likely to be effective in increasing sodium excretion [285] After three or four days increased glutaminase activity produces increased ammonia [88, 26] which then can combine with the chloride or other acidic ion and thus conserves sodium

Two to 3 gm (30 to 45 grains) of ammonium chloride three times daily are often administered orally for the two days preceding each injection of Mercuhydrin This is given in the form of compressed tablets of 0 4 gm (6 grains) each (i e five to eight tablets three times daily) or of keratin coated capsules of 0 5 gm (7½ grains) each (four to six tablets three times daily) In the intervals the ammonium chloride is discontinued to avoid nausea, vomiting or severe acidosis The acidifying salts are contraindicated in patients with renal impairment Prolonged use of ammonium chloride with the mercurials may cause potassium depletion and hypokalemia Occasionally I have seen prolonged use of ammonium chloride cause severe acidosis with intense dyspnea which was mistaken for the dyspnea of intractable heart failure The clinical picture is characterized by anorexia, nausea, vomiting, lassitude progressing to marked stupor, areflexia and Kussmaul respiration [26] and may simulate a cerebrovascular accident [30] The blood plasma shows an elevated chloride and reduced bicarbonate (hyperchloremic acidosis) (see Fig 61) and moderate azotemia A similar blood electrolyte spectrum is produced by cationic resins and Diamox Hyperchloremic acidosis from ammonium chloride therapy is most apt to occur in the presence of intrinsic renal disease as indicated by constant, marked albuminuria and a fixed low specific gravity Hyperchloremic acidosis is treated by the intravenous administration of isotonic (5%) sodium bicarbonate or ⅙ molar sodium lactate

XANTHINE DERIVATIVES

The xanthine derivatives (purines) are now of limited use as diuretics because of their uncertain effectiveness and the decisive superiority of the mercurial salts The xanthine derivatives may be worthy of trial when the mercurials are not tolerated They possess the advantage that they may be taken orally The exact mode of diuretic action of the xanthines is uncertain—increase in glomerular filtration decrease in tubular reabsorption, increased blood flow and other mechanisms having been invoked [37, 41, 201] Following the intravenous administration of aminophylline to 45 patients with myocardial insufficiency Green and associates[11] observed an average increase in cardiac output of 12 per cent with a range of plus 185 to minus 45 per cent There was a more impressive increase in sodium and water excretion, especially the former Renal clearance data indicated that the heightened excretion of sodium was due to a diminution in tubular reabsorption of this ion Similarly Davis and Shock[31] noted a variable increase in renal plasma flow and glomerular filtration rate with a more prominent and sustained increase in sodium clear

ance They therefore concluded that the latter was a result of a decreased tubular reabsorption of sodium

The most effective diuretic of this group is theophylline (Theocin)[187] while theobromine theobromine sodiosalicylate (Diuretin) and caffeine have weaker actions Theophylline ethylenediamine (aminophylline) in doses of 0 1 to 0 2 gm three or four times daily Theocalcin (theobromine calcium salicylate) in doses of 1 0 gm four times daily Theesodate (theobromine sodium acetate) in doses of 0 5 gm four times daily and theophylline (Theocin) 0 2 gm four times daily are among the commonly employed xanthine diuretics But the effectiveness of aminophylline administered orally is unpredictable because of uncertain absorption or its destruction by the liver For this reason rectal administration by suppository and especially intravenous injection have been employed to circumvent the liver and these routes of administration are more effective Choline theophyllinate in doses of 50 to 400 mg (average 200 mg) three or four times daily was reported to abolish the need for mercurials or reduce their frequency at least 50 per cent in 28 out of 45 patients with congestive heart failure[3] Except in very occasional instances I have found no need for the xanthine diuretics when the mercurials can be used However the intravenous administration of aminophylline (0 25 or 0 5 gm in 10 cc) is very effective in controlling Cheyne-Stokes respiration associated with heart failure and aminophylline suppositories containing 0 3 to 0 5 gm of aminophylline inserted before retiring sometimes help to avoid paroxysms of nocturnal dyspnea The control of Cheyne-Stokes respiration by aminophylline is not due to increased cerebral blood flow as was formerly believed since actual measurements by the nitrous oxide method revealed that aminophylline depressed cerebral blood flow[249] It has been suggested that aminophylline stimulates the respiratory center directly or indirectly by increasing the medullary carbon dioxide

Headache nervousness nausea and vomiting abdominal cramps and diarrhea are common symptoms of sensitivity to the xanthine derivatives especially if given in full therapeutic doses Epilepsy is a contraindication to these drugs as they are said to irritate the cerebral cortex and precipitate convulsions in susceptible individuals Sometimes the toxic symptoms of the purines can be prevented by combining each dose with ¼ to ¾ grain of phenobarbital

URACILS

The uracils are related compounds (ureide dihydroxypyrimidines) which have been investigated as possible oral diuretics While some of them have produced a satisfactory diuretic effect in cardiac patients[175, 191] presumably by inhibiting tubular reabsorption of sodium[191] they have not gained clinical acceptance chiefly because of the high incidence of gastrointestinal and other symptoms[191] One of the uracil derivatives Mictine (brand of aminometramide), has been recently made commercially available in 200 mg tablets It is recommended in doses of four to six tablets daily with meals for initial and continuing diuresis and one to four tablets daily for maintenance

UREA

When renal function is intact and other diuretics are no longer effective or cannot be given urea is sometimes of distinct value as a diuretic Satisfactory results have been reported by Miller and Feldman[48] who administered urea for long periods to the same patients Important objections to this substance are the nauseating taste and the tendency to cause vomiting or extreme thirst I have seen excellent clinical results on occasion but have utilized it rarely in recent years

Large doses of urea (45 to 90 gm daily) must be given usually in divided doses two to four times daily Various efforts not too successful have been made to disguise its taste It has been given in ice cold water in grape juice in beer and in mixtures containing syrup of acacia I have found urea to be taken best as an effervescent mixture made as follows

℞		gm or cc
Urea	℥ xvi	480 0
Saccharin	gr vi	0 7
Potassium bicarbonate	℥ xii	48 0
Citric acid	℥ xiii ss	55 0
Tartaric acid	gr xxx	2 0
Oil of peppermint	gtt vi	0 4

M Sig One or two ounces dissolved in water three times daily Drink slowly while effervescing

POTASSIUM SALTS

Potassium salts have been used as diuretics, especially in combination with restriction of sodium chloride and fluids [193] They are contra indicated in the presence of renal insufficiency There is also evidence that patients with severe heart disease do not handle a potassium load normally [47] Therefore there is some risk in inducing dangerously high plasma potassium levels Potassium chloride is usually given in doses of 2 to 4 gm three times daily To avoid gastric irritation it is usually given in enteric coated tablets The cardiac toxicity of potassium salts is discussed on page 1030

ALCOHOL[250]

Alcohol has a specific diuretic action, probably the result of decreased secretion of antidiuretic hormone since alcohol diuresis is inhibited by pitressin [100] In addition water and other liquids taken with alcohol account for some of the diuretic effect

OTHER DRUGS

Morphine

Next to digitalis and the mercurial diuretics morphine is the most useful drug in the treatment of congestive heart failure Its chief value and indication are in the management of the acute episodes associated with heart failure Under such circumstances the therapeutic benefits of morphine are often brilliant and appear with striking speed Morphine is administered for the relief of various forms of dyspnea, especially cardiac asthma and pulmonary edema but also for severe dyspnea at rest and orthopnea associated with left sided heart failure Each dose of morphine should be individually ordered by the physician Standing orders for repeated doses of opiates occasionally lead to serious overdosage or addiction When dyspnea becomes persistent, the danger of morphine addiction must always be borne in mind, the drug must be either withheld or administered in small doses of 0 007 to 0 010 gm (1/8 to 1/6 grain) Often these doses accomplish as much as can be expected from the use of morphine in cases of congestive heart failure Even when care is exercised morphine addiction is not rare because the unequalled though temporary, relief attained with this medicament leads to its continued usage

The action of morphine, in so far as it relieves the symptoms of congestive heart failure, is not altogether certain In the first place it depresses the respiratory center and interferes with the reflex which causes hyperventilation and dyspnea (see p 191) At the same time it probably reduces the venous return to the heart, thereby diminishing the output of the right ventricle and consequently also the intense pulmonary congestion which is the basis of dyspnea The diminution in ventilation reduces the work of the respiratory muscles The elimination of the patient's restlessness and anxiety is also an important effect of morphine serving to improve the patient's comfort On the unfavorable side is the antidiuretic effect of morphine in patients with heart failure,[11] but this is rarely of practical importance

If the patient is suffering from moderate continuous dyspnea at rest and orthopnea he should be given 0 010 gm (1/6 grain) of morphine or 5 minims of a 3 per cent aqueous solution hypodermically This should be repeated morning and evening for a day or two until rest, digitalis and diuretics become effective If the dyspnea is acute or severe, the dosage may have to be increased to 0 015 gm (1/4 grain) or 0 5 cc (7½ minims) of the 3 per cent solution If the patient is experiencing an attack of cardiac asthma or acute pulmonary edema the dose should be between 0 015 and 0 020 gm (1/4 to 1/3 grain), depending on the severity of the attack If immediate relief is urgent, the morphine should be given intramuscularly or 0 010 gm (1/6 grain) should be injected intravenously, since the effect of morphine administered subcutaneously may not appear for one half hour or more If the patient had been suffering from recurrent attacks small doses of morphine may be given prophylactically for a few days, usually before the patient retires in the evening As a rule, 0 006 to 0 010 gm (1/10 to 1/6 grain) of morphine hypodermically or 0 010 to 0 015 gm (1/6 to 1/4 grain) by mouth will suffice But this is rarely necessary if digitalization sodium restriction mercurial diuretics and oxygen therapy are properly employed Meperidine (Demerol) is useful for analgesia, but does not depress the respiratory center in therapeutic doses and therefore is not a substitute for morphine in the relief of dyspnea

Codeine

Codeine sulfate in doses of 0 03 to 0 06 gm (½ to 1 grain) hypodermically may oc

casionally be substituted satisfactorily for morphine in treating patients with chronic dyspnea. The chief value of this drug, however, is to control the cough due to pulmonary congestion and infection. The dose is 0.015 gm (1/4 grain) by mouth every three to four hours, but larger doses may be needed. Hycodan bitartrate in doses of 0.005 to 0.01 gm (1/12 to 1/6 grain) is at least as effective in controlling cough and is less constipating than codeine. The medication should be given at night or repeated throughout the day if necessary.

Sedatives

Bromides in doses of 10 to 15 grains three times daily, chloral in doses of 5 to 15 grains, or combinations of the two in smaller dosage, or phenobarbital in doses of 0.015 to 0.03 gm (1/4 to 1/2 grain) three times daily are valuable as sedatives to allay restlessness and anxiety. Soporifics such as Nembutal (1½ to 3 grains), Seconal (1½ to 3 grains), Ipral (2 to 4 grains) or Veronal (5 to 10 grains) may be necessary to induce sleep. If insomnia is due to cough, codeine is necessary, either in place of or in combination with soporifics.

Antibiotics

Bronchopulmonary infections occur commonly in the congested lungs of patients with heart failure. They often account for the unexplained fever observed in many cases of heart failure, but it may be difficult to distinguish the signs of congestion from those of pneumonia. The use of antibiotics is often justified on an empiric basis in patients with heart failure who are febrile or experience cough out of proportion to the degree of pulmonary congestion, especially if the cough is not relieved by antidiuretics. The incidence of pulmonary infection as a contributory or primary cause of death in heart failure has diminished greatly since the widespread employment of antibiotics. Because of these observations it has been suggested that broad spectrum antibiotics be administered prophylactically for prolonged periods to patients with heart failure, especially old people.[237]

Dicumarol

This drug has been administered in order to reduce the frequency of thromboembolic complications in heart failure and beneficial results have been reported.[255] (For method of administration see p. 577.) Patients with congestive heart failure, especially those subjected to prolonged bed rest, are particularly susceptible to venous thrombosis and pulmonary emboli. If the reported favorable results of anticoagulants in the treatment of acute myocardial infarction may be applied to cases of congestive heart failure, anticoagulants should be equally effective in heart failure. Several reports of controlled series of cases of heart failure[267, 2, 359] treated with and without anticoagulants have indicated that the incidence of thromboembolic complications and the mortality rate in those patients receiving anticoagulants were reduced by as much as one third to one half of those in control patients. Because of impaired hepatic function in congestive heart failure (p. 151), the prothrombin time is often prolonged and the patient may be excessively sensitive to anticoagulants. Therefore, the prothrombin time should be determined before anticoagulants are administered as well as repeatedly during anticoagulant therapy. Although anticoagulants would appear to be of promising value in congestive heart failure, the difficulty of convincing many physicians of their value in myocardial infarction despite impressive statistical evidence in their favor suggests that it will be even more difficult to obtain convincing evidence of their benefit in heart failure.

Hypotensive Drugs

Ganglion blocking hypotensive drugs used in the treatment of hypertension were noted to ameliorate associated congestive heart failure.[57] A reduction in pulmonary congestion and dyspnea and an increase in vital capacity were noted, as well as a diminution in cardiac size and improved exercise tolerance after the administration of pentamethonium to hypertensive patients with heart failure.[303] Kelley et al.[195] reported that the slow intravenous administration of 30 mg of hexamethonium in 19 patients with various types of heart disease and heart failure reduced the elevated venous pressure as well as the right atrial, right ventricular and pulmonary arterial pressures, shortened the circulation time and effected symptomatic improvement in the degree of dyspnea and orthopnea. They suggested that the beneficial action of hexamethonium in heart failure was due both to a diminution in peripheral resistance, reducing the work demand of the left ventricle, and to a lowering of the filling pressure of the right heart, permitting it to contract more effectively. Similar observa

tions were made by Shuman and associates[299] in 21 patients with congestive heart failure due to hypertension, coronary arteriosclerosis and valvular heart disease, following the administration of tetraethylammonium bromide and hexamethonium iodide Hexamethonium may also be useful in the treatment of paroxysmal dyspnea or pulmonary edema in patients with mitral stenosis and pulmonary hypertension, since it may reduce the pulmonary artery pressure without diminishing the cardiac output [79, 104a]

Laxatives and Cathartics

When patients are ambulant regular bowel action should be induced by habit formation with or without the aid of mineral oil If this does not succeed or if patients are confined to bed it is necessary to maintain regular bowel movements by mild cathartics or laxatives Milk of magnesia (1 to 2 oz), cascara sagrada (5 to 10 grains) or compound licorice powder (2 to 3 teaspoonfuls) is usually adequate Magnesium sulfate (½ oz), given every few days has been found useful when patients are edematous due theoretically to the loss of fluids associated with the catharsis Cathartics acting on the colon should not be administered to patients receiving oral mercurial diuretics (see p 282) The possibility of potassium depletion due to drastic catharsis should be considered Occasionally glycerin suppositories or small oil saline or sodium bicarbonate enemas are useful, but they should be avoided if they weaken the patient unduly An occasional colon irrigation when properly performed tires the patient less than an enema and relieves abdominal distention as well as constipation Some patients undergo more physical and mental strain in trying to use the bedpan than when helped to the toilet or preferably to a commode at the side of the bed For such patients the physician should employ his good judgment in determining whether the use of the bedpan is absolutely essential

Brandy sherry or nux vomica may be useful in treating patients who are depressed or suffer from weakness and anorexia The alcoholic beverages may be especially helpful for elderly patients and those with coronary heart disease

Hypertonic solutions of dextrose (50 cc of 50 per cent 125 cc of 20 per cent or 250 cc of 10 per cent solution) or of sucrose may be given intravenously in attacks of pulmonary edema and to promote diuresis The carbohydrates have also been considered of therapeutic benefit because they improve the nutrition of the heart

OXYGEN THERAPY AND POSITIVE PRESSURE RESPIRATION[57, 28]

Oxygen administered in high concentrations (40 to 50 per cent or higher), by means of special masks, tents or nasal catheter, may be of great symptomatic value in some cases of congestive heart failure According to Barach and his associates,[5] who have been the most ardent advocates of this therapeutic measure, the depressed oxygen saturation of the arterial blood is restored to normal dyspnea and cyanosis are relieved the lactic acid content of the blood is diminished diuresis effected and edema reduced In my experience oxygen therapy is of limited value for the fundamental manifestations of congestive heart failure but may be of great benefit in treating associated symptoms or complications It was shown above (p 190) that the arterial blood of patients with congestive heart failure usually has a normal oxygen saturation so that further oxygen administration has no theoretical indication in most cases But aside from any increase in the oxygen carried by hemoglobin increased oxygen concentration in the inhaled air results also in an increased concentration of oxygen dissolved in plasma and available for greater oxygen supply to the tissue Actually many patients report subjective improvement with oxygen therapy High concentrations of oxygen are indicated chiefly in the relatively small percentage of cases of congestive heart failure in which the oxygen content of the arterial blood is diminished and in patients with pulmonary edema or other associated pulmonary disease or complications Usually but not always, such cases are recognizable by the presence of cyanosis but a therapeutic trial is desirable if there is any doubt If oxygen must be administered continuously for many days, a tent is usually preferable to the mask since the administration of pure oxygen is irritating unless it is hydrated At an oxygen inflow of 8 to 10 liters per minute oxygen concentrations of 40 to 45 per cent can be maintained in the tent The air cooling effect of oxygen by tent is often beneficial in warm weather, since patients with congestive heart failure cannot tolerate excessively warm atmospheres [19]

The cases of congestive heart failure in which oxygen therapy is indicated usually include the following

(a) Congestive heart failure of rheumatic coronary atherosclerotic hypertensive or syphilitic etiology complicated by pulmonary lesions such as infarcts pulmonary edema lobar or bronchopneumonia

(b) Congestive heart failure secondary to bronchopulmonary disease such as pulmonary fibrosis of varied etiology and pulmonary emphysema in which there is no significant carbon dioxide retention

(c) Congestive heart failure associated with acute coronary thrombosis

The administration of oxygen in the ordinary manner can hardly be expected to affect the arterial blood when it is normally saturated with oxygen But the inhalation of oxygen or air under a positive pressure of 5 to 8 mm Hg may be beneficial even in such cases[4] For then the arterial oxygen content may be even greater than normal because the oxygen content of the plasma is increased the oxygen combined with the hemoglobin being of course unchanged Barach[4] reported a clearing of pulmonary edema due to heart failure presumably because the oxygen introduced offers an opposing pressure to the increased pulmonary capillary pressure and thus retards the exudation of plasma from the capillaries into alveoli The oxygen causes a positive pressure within the chest which retards the entrance of blood into the right heart and therefore into the lungs In patients with acute left heart failure diminution of the venous return may act like a phlebotomy to permit recovery of cardiac function and increase in cardiac output Helium-oxygen mixtures are often used with positive pressure breathing because of the lower specific gravity of helium *Thus much less effort is required* than for the breathing of air or pure oxygen

When oxygen is administered in concentrations of 90 to 100 per cent it is irritating to the mucosa of the respiratory tract and may induce coughing It diminishes pulmonary ventilation which may be physiologically undesirable although symptomatically advantageous In cases of heart failure due to cor pulmonale oxygen concentrations of 40 to 50 per cent may be dangerous and even fatal because the oxygen removes the needed respiratory stimulus of anoxia depresses respiration and causes elevation of the blood carbon dioxide to toxic level (p 993)

PHLEBOTOMY (VENESECTION)

The removal of 350 to 1000 cc of blood from the vein of a patient with congestive heart failure may rapidly and dramatically relieve dyspnea orthopnea cyanosis systemic venous and hepatic engorgement Phlebotomy is indicated chiefly when there is intense pulmonary engorgement (especially with pulmonary edema) due to left-sided heart failure But it is also useful in cases of right sided heart failure in which there is an extreme elevation of the venous pressure and associated manifestations of systemic engorgement Phlebotomy is often a life-saving measure when the patient suffers from acute pulmonary edema Phlebotomy should also be performed when morphine and other therapeutic measures fail to control an attack or recurrent attacks of cardiac asthma

In cases of right sided heart failure with high venous pressure phlebotomy markedly reduces the pressure and often relieves symptoms but the therapeutic results are rarely as striking as in cases of acute left sided heart failure The symptomatic improvement after phlebotomy usually occurs with incredible speed often when the needle is still in the vein For phlebotomy in cor pulmonale see page 994

The removal of less than 350 cc of blood is rarely useful, larger amounts (up to 1000 cc) should be withdrawn if no benefit is obtained especially if the patient is a large person has an increased blood volume is hypertensive and if his blood has a satisfactory hemoglobin content Phlebotomy is rarely justified if the patient is anemic The phlebotomy should be performed by introducing a needle of large bore such as is used for transfusions connected with a 6 inch rubber tube by an adapter A free flow should be obtained to avoid clotting In an emergency the vein may have to be cut with a sterile scalpel

Phlebotomy relieves the symptoms of congestive heart failure by reducing the circulating blood volume and consequently the venous return to the right side of the heart This reduces the right ventricular output into the congested lung The overloaded and failing left heart can then increase its cardiac output and relieve the pulmonary

congestion[182] In contrast to the emergency benefit of a needed phlebotomy is the subsequent regret at the loss of oxygen carrying capacity of the blood Therefore the indication for phlebotomy should be unequivocal The cautious replacement of packed erythrocytes may have to be considered after the acute disturbance has been definitely controlled

Tourniquets

Effects similar to phlebotomy may be obtained by the temporary application of tourniquets or blood pressure cuffs to all four extremities[97] Dramatic improvement may follow this procedure in cases of paroxysmal dyspnea or pulmonary edema due to acute left ventricular failure This procedure should always be tried before a phlebotomy is performed However tourniquets should be applied only for limited periods (15 to 30 minutes) to any given extremity The tourniquets on each one of the four extremities should be serially removed for brief intervals The application of tourniquets decreases the venous return and affords relief but the cardiac output may be reduced so markedly that shock is induced

MECHANICAL REMOVAL OF SEROUS EFFUSION AND EDEMA FLUID

Thoracentesis

It is often necessary to remove pleural effusions in cases of congestive heart failure Thoracentesis is indicated when the effusion is large and is causing or contributing to dyspnea It is sometimes difficult to ascertain the exact importance of a pleural effusion in the production of this symptom When other therapeutic measures fail to relieve dyspnea, the removal of fluid from the chest is often indicated even when the size of the effusion does not appear to be very large I use an airtight Potain set by means of which the effusion is removed by suction into a bottle containing a partial vacuum The patient lies on his side, with the side to be tapped uppermost The needle is introduced posteriorly near the lower end of the effusion the site of which has been localized by percussion or roentgen ray examination Usually 500 to 1000 cc but not more than 1500 cc is removed The procedure should be stopped if the patient becomes dyspneic coughs or has pain in the shoulders Repeated aspirations of fluid from the pleural space have been effective in the removal of previously resistant edema[284]

Abdominal Paracentesis

Only occasionally must ascitic fluid be removed in cases of congestive heart failure, and much more rarely since the use of the powerful mercurial diuretics Abdominal paracentesis is indicated when the peritoneal effusion is sufficient to cause symptoms such as dyspnea and distention despite all other medical therapy

The patient, after voiding sits up in bed with his feet hanging over the side of the bed onto a chair The skin of the lower half of the abdomen is cleaned and the site of injection is sterilized and infiltrated with 2 per cent procaine This site is in the linea alba midway between the umbilicus and symphysis pubis Through the anesthetized area a 1 inch incision is made with a scalpel through the skin and fascia A trocar and cannula are introduced by way of the incision through the fascia and into the abdominal cavity The trocar is withdrawn and the ascitic fluid allowed to run out of the cannula and connecting tubes into large flasks When the fluid stops draining a sterile dressing and adhesive tape are placed over the incision and a broad, tight abdominal binder is applied

Mechanical removal of subcutaneous edema is rarely necessary since mercurial diuretics have become available If essential, the surgical insertion of Southey tubes or multiple incisions of the skin and subcutaneous tissue, usually of the legs, may effectively remove large quantities of fluid[173, 314] Aseptic technique should be employed even though the danger of infection is less than in cases of nephrotic edema The prophylactic administration of penicillin is justifiable Massive edema of the scrotum should be treated by elevation with a Bellevue bridge and if necessary by multiple incisions

LIGATION OF THE INFERIOR VENA CAVA

I have formerly employed ligation of the inferior vena cava in patients with heart failure primarily to prevent pulmonary emboli arising in venous thrombi in the legs Such emboli are relatively frequent in advanced heart failure, and may be responsible for it being refractory to conventional treatment Ligation of the inferior vena cava has also been suggested[79] for its more direct beneficial effect in advanced failure Such ligation, acting as a chronic internal tourniquet, impairs the venous return and relieves the overburdened

heart which then increases its cardiac output According to Cossio and Perianes[79] the benefit of inferior vena caval ligation depends also on improved lymphatic circulation Pulmonary hypertension is said to be relieved Clinically the symptoms and signs of both left and right-sided heart failure may be ameliorated Favorable results in 55 to 65 per cent of large series of cases of heart failure treated by inferior vena caval ligation have been reported by South American and French physicians [81, [illegible], 83] In the earlier reports the mortality rate was 20 to 25 per cent but this has been substantially diminished [4] I have resorted to inferior caval ligation only occasionally since oral anticoagulants have been used extensively and since surgical procedures on the heart especially mitral commissurotomy have been available In some of the cases in which I have recommended inferior vena caval ligation for refractory heart failure associated with suspected recurrent pulmonary emboli the results were spectacularly beneficial I have always presumed that the clinical improvement was due to cessation of pulmonary embolization but it may have been due also to relief of overloading of the circulation by diminishing the venous return Ligation of the inferior vena cava may be regarded as a palliative procedure in intractable heart failure especially when accompanied by pulmonary emboli [82]

TOTAL THYROIDECTOMY ANTITHYROID DRUGS RADIOIODINE

Thyroidectomy was suggested as a means of treating congestive heart failure in the hope that by lowering the basal metabolism i e the oxygen requirement and other needs of the tissues the slow inadequate circulation would then be sufficient for the lesser demands made upon it Furthermore the cardiac output and the work of the heart would be diminished Subtotal thyroidectomy often gave brilliant results in cases associated with hyperthyroidism but was ineffective in other cases of congestive heart failure Blumgart and his associates[88] suggested and performed total thyroidectomy for the treatment of congestive heart failure (and angina pectoris for which see p 483) The operation was restricted to those patients who were reasonably good surgical risks and suffered from intolerable congestive heart failure which had not responded to any or all of the measures discussed above The results obtained have not been sufficiently striking to justify use of such a drastic operation

Thiouracil and Other Antithyroid Drugs

The same principle underlying total thyroidectomy for heart failure has suggested the use of antithyroid drugs to lower the metabolism and thus reduce the work of the heart Sharpey-Schafer [95] reported prolongation of life by the use of 60 to 120 mg daily of thiouracil in patients whose heart failure had not responded to the usual therapy In seven to ten days there was a reduction in basal oxygen consumption a fall in venous pressure an augmentation of cardiac output and increased exercise tolerance

Radioactive Iodine (I^{131})

Blumgart and associates[88] *and Jaffe et al* [89] employed radioactive iodine (I^{131}) in euthyroid patients with heart failure for the purpose of lowering their metabolism and the work imposed on the heart [88] Blumgart et al [89] presented a summary of the results in the treatment with radioactive I^{131} of 1070 euthyroid patients with congestive heart failure or angina pectoris 87 from their own series and 983 reported by questionnaire from 49 other clinics Three hundred and fifty of the total represented cases of heart failure Treatment was confined essentially to patients who were incapacitated or unable to work despite the use of all available medical measures Three weekly doses of 20 millicuries of I^{131} or less (10 to 20 mc) are given to euthyroid patients Transitory thyroiditis and hypermetabolism may develop in the second and third week of treatment in about one third of the patients After the third dose additional doses are given at intervals of one to two months if necessary until myxedema appears Eight weeks to six months are required before the desired degree of hypothyroidism is produced Diminution of dyspnea and orthopnea usually occur at the time of onset of clinical hypothyroidism Thereafter a daily dose of desiccated thyroid (6–12 mg) is administered the dose being adjusted to obtain the lowest tolerable basal metabolic rate necessary to obtain relief of the heart failure without undue discomfort from myxedema As a rule a basal metabolic rate between −20 and −25 was satisfactory and a daily dose of 6 to 30 mg of thyroid extract Occasionally regeneration of thyroid tissue caused an exacerbation of symptoms and ne-

cessitated withdrawal of thyroid with subsequent retreatment with I^{131} The clinical results were quite favorable, about 60 per cent showing worthwhile results, of these about 20 to 25 per cent were considered excellent and 35 to 40 per cent good The remainder failed to show improvement The results in the treatment of heart failure were not as striking as in the treatment of angina pectoris (p 483)

Similar favorable results in 78 euthyroid patients with advanced heart failure were reported by Jaffe et al [185] who administered 6 millicuries of I^{131} orally each week until the patient had received 30 millicuries of radioiodine A second or third course was sometimes necessary They reported excellent results in 53 per cent, good results in 28 per cent and no improvement in 19 per cent

Although these results appear promising, the induction of myxedema in euthyroid patients cannot be regarded as a routine form of treatment even in patients with severe congestive heart failure *The procedure is unphysiologic* and adds another disease requiring continued therapy In many instances there is *uncertainty as to whether the improvement is* due to the radioactive iodine, to other measures simultaneously employed (e g better control of rest, *digitalization, restriction of* sodium intake) or to the natural variations in the disease Nevertheless, the administration of radioiodine to induce myxedema should be undertaken when severe recurrent pulmonary edema or chronic severe congestive heart failure does not yield to any other available form of therapy after prolonged and meticulous *trial In my experience the radioiodine treat*ment of congestive heart failure has not afforded impressive or consistent therapeutic results

EMERGENCY TREATMENT OF ACUTE LEFT VENTRICULAR FAILURE (CARDIAC ASTHMA PULMONARY EDEMA)

An effort should be made to determine the underlying cause and precipitating factors as these may modify management Thus if pulmonary edema is associated with acute coronary occlusion and shock, phlebotomy is rarely if ever part of the treatment On the other hand, the indication for phlebotomy may be especially strong if the attack is precipitated by excessive intravenous infusions *or transfusion* Rapid intravenous digitalization with ouabain may be the prime therapeutic agent if acute left ventricular failure results from the sudden onset of atrial fibrillation with a very rapid ventricular rate When acute left ventricular failure is *precipi*tated by some other paroxysmal tachycardia the former may be most effectively controlled by checking the paroxysm with *carotid sinus* pressure digitalization, quinidine or other agents as discussed in Chapter 14 In the presence *of pneumonia or other serious infec*tion prompt and adequate antibiotic therapy may be essential to the control of pulmonary edema

In general, morphine is administered in doses of 10 to 20 mg (1/6 to 1/3 grain) subcutaneously intramuscularly or occasionally intravenously, according to the urgency of the situation Atropine may be combined in doses of 0 4 to 0 6 mg (1/150 to 1/100 grain) if tachycardia is not a prominent feature Aminophylline (0 25 to 0 5 gm) should be infused intravenously at a slow rate If excessive respiratory *depression results from morphine* or other opiates, give 15 mg Nalline subcutaneously and repeat at 20 minute intervals *until patient is aroused The patient should be* propped up high in bed or be permitted to sit with support while his feet hang down from *the side of the bed or the head of the bed is* raised by blocks Oxygen therapy should be given promptly preferably under slight posi*tive pressure (4 to 8 cm of water)*[4] *if shock is* absent Helium-oxygen mixtures are preferred if available [5] The oxygen under pre*sure increases intra alveolar pressure* and prevents transudation of fluid from the alveolar capillaries Tourniquets should be applied serially *to the four extremities* with periods of release If there is no contraindication, the patient should be rapidly digitalized intravenously *if the emergency demands it* *Ouabain or Cedilanid* is administered intravenously as described previously (p 263) Because *respiratory obstruction in acute pul*monary edema may be intensified by the mechanical interference of foam due to edema fluid *inhalation of antifoaming agents* has been utilized[2,9] Usually 50 per cent ethyl alcohol is employed as the antifoaming agent but *the synthetic 2-ethylhexanol is* said to be much more rapid acting [70] The nebulized antifoaming drugs are administered by mask, by *bubbling oxygen with a positive* pressure apparatus through the drugs in a humidifier *Hexamethonium*, which reduces

the peripheral arteriolar resistance may be worthy of trial in cases of pulmonary edema in patients with severe hypertension but even when the heart failure is not associated with hypertension [351, 73, 104] If these measures are ineffective and there is evidence of an increased venous pressure and a high blood volume a phlebotomy should be performed (p 289) Other measures will be determined by the underlying disease and the precipitating factor

In cases of cardiac asthma of moderate severity or of mild pulmonary edema not all of these measures are necessary Assumption of the upright position and the injection of morphine may suffice Not infrequently the patient spontaneously sits up or jumps up out of bed to stand or sit near a window and is better before the physician arrives Nitroglycerin 0 6 to 1 2 mg (1/100 to 1/50 grain) administered sublingually afforded prompt relief of nocturnal dyspnea in 10 patients with left ventricular failure without angina pectoris according to Johnson et al [197] Only if these measures are inadequate should the physician successively add the application of tourniquets oxygen therapy the administration of aminophylline and digitalis etc

Prophylactic measures to prevent recurrence may include sleeping with the head elevated (cardiac bed) careful sodium restriction the use of diuretics and digitalization avoidance of excessive and sudden physical exertion the control of cough and the use of anticoagulants if the attack is precipitated by an embolism Pulmonary edema may be avoided in cardiac or elderly subjects if caution is used in the administration of intravenous infusions and the use of sedimented ("packed") erythrocytes instead of whole blood for transfusions [11] The patient's head and shoulders should be raised during the infusion or transfusion Recurrent pulmonary edema in patients with mitral stenosis is usually an indication for mitral commissurotomy For treatment of shock with pulmonary edema in acute myocardial infarction see page 566

TREATMENT OF INTRACTABLE HEART FAILURE [309, 268, [illegible], 306]

Despite all the therapeutic measures detailed in this chapter patients sometimes do not respond or cease to respond and the manifestations of heart failure persist or progress This state of unresponsiveness is often termed refractory or intractable heart failure When confronted with what is apparently intractable heart failure the physician should critically and systematically review the case for both a possibility of error in diagnosis and possible deficiencies or complications of treatment

Review of Accuracy of Diagnosis

The diagnosis of heart failure is based essentially on two manifestations dyspnea and edema and their variants Therefore it is necessary to exclude the numerous diseases which can produce dyspnea or other evidences of abnormal water retention Various bronchopulmonary diseases metastatic carcinomatosis various forms of anemia especially that due to chronic gastrointestinal bleeding hepatic and renal disease are among the more common conditions which produce clinical features simulating heart failure Definite evidence of underlying cardiac disease cardiac enlargement prolongation of the circulation time and elevation of the venous pressure in the upper and lower extremities are important features supporting a clinical diagnosis of heart failure

Remediable Factors Responsible for Persistent Heart Failure

A search should be made for possible factors responsible for precipitating heart failure or for rendering it refractory to treatment especially since some of them may be eliminated or ameliorated Among these are (1) hyperthyroidism (2) anemia (3) beriberi (4) arteriovenous fistula (5) arrhythmia with tachycardia (6) rheumatic fever (7) bacterial endocarditis (8) pulmonary embolism (9) hypertension (10) hepatic cirrhosis In particular in my experience masked hyperthyroidism and constrictive pericarditis are overlooked and are responsible for persistent symptoms of heart failure Both conditions are curable with dramatic improvement of the heart failure On the other hand if overlooked they prevent alleviation of heart failure despite the most vigorous exercise of all conventional therapeutic agents Not infrequently persistent heart failure is due to recurrent pulmonary emboli and relief of the heart failure may be obtained if embolization is prevented by the use of anticoagulants or by ligation of the veins of the lower extremity or of the inferior vena cava Similarly anemia thiamine deficiency and in

fection, especially of the pulmonary or urinary tract, should be sought and corrected, if possible When persistent heart failure is directly or indirectly due to mitral stenosis, coarctation of the aorta patent ductus arteriosus, other surgically correctible congenital cardiovascular anomalies or pheochromocytoma, the feasibility of operative correction should be considered

Adequacy of Therapy of Heart Failure

Ordinarily heart failure may be alleviated with moderate restriction in activity, digitalization and moderate reduction in sodium intake Many imperfections in treatment will not necessarily prevent a favorable therapeutic result But in cases of intractable heart failure it is essential that every therapeutic measure be carried out with the most meticulous perfection in order to succeed The limitation of the patient s activity or the completeness of his bed rest may be inadequate for the severity of the heart failure When heart failure appears intractable, it is particularly important that sodium restriction should be strict, i e not more than 200 to 500 mg sodium daily and that adherence to the diet be carefully checked The occasional response of purported cases of intractable heart failure after a few days of hospitalization is usually due to stricter bed rest or better control of low sodium intake Sometimes rigid restriction of sodium intake is best effected by the use of the Kempner rice-fruit diet or by combining a low sodium diet with cationic exchange resins

Intractable heart failure is rarely due to inadequate digitalization, not uncommonly, however to overdigitalization especially in patients with heart failure and sinus rhythm This should be checked by careful review of dosage clinical features and electrocardiograms

Occasionally apparently intractable heart failure is controlled by more frequent administration of mercurial diuretics or by combining the mercurials with adjuvants such as ammonium chloride aminophylline or Diamox The use of opiates or barbiturates may interfere with mercurial diuresis Large pleural effusions or ascites should be tapped Sometimes too much emphasis is placed on one or another therapeutic agent to obtain relief of intractable heart failure with neglect of other therapy Success often depends on the simultaneous attention to all possible measures Thus increasing frequency of injection of mercurials may succeed only if sodium intake is adequately restricted or only after adequate sodium restriction and bed rest, or only after these measures plus cationic resins, ammonium chloride, aminophylline and Diamox are all utilized in combination

Intractable heart failure is often noted at the same time that there are abnormalities in the blood electrolyte pattern (p 275) Because of this ammonium chloride may be administered when there is evidence of hypochloremic alkalosis or hypertonic sodium chloride when there is severe hyponatremia Occasionally these measures result in clinical improvement But most often the electrolyte disturbances are the result of the same disturbances that produced the intractable heart failure rather than the cause One should be careful not to exaggerate the importance of chemical changes in the blood presumed to be due to too vigorous therapy when the error lies in inadequate utilization of available therapeutic measures overlooked infection improper antibiotic overdigitalization or uncontrolled pulmonary embolization The use of mercurial diuretics and the increased understanding of the application and effectiveness of *very low* sodium diets are two of the most important advances in the therapy of heart failure It would represent a step backward to surrender the advantages of these measures because of an exaggerated emphasis on occasional dangers of sodium "depletion" or hyponatremia Finally, it must be recognized that sooner or later heart failure *becomes intractable because of the advanced* and irreversible nature of the cardiac disability This admission can be made only after every effort has been made to carry out all available therapeutic measures as indicated

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Chapter 12

ACUTE CIRCULATORY FAILURE SHOCK, SYNCOPE AND SUDDEN DEATH

Acute and Chronic Circulatory Failure

Circulatory failure has been defined as the inability of the circulation to maintain an adequate minute volume blood flow to supply the needs of the tissues In the preceding chapters I have discussed chronic circulatory failure (congestive heart failure) in which the deficiency in cardiac output is gradual in development and moderate in degree Compensation is effected at first by cardiac enlargement and later by a variety of adjustments which tend to restore an adequate cardiac output Many of the manifestations of chronic circulatory (congestive heart) failure are due, not to the inadequate output per se, but to the consequent pathologic physiologic adjustments such as sodium and water retention and increased circulating blood volume

This chapter is concerned with the more acute forms of circulatory failure in which the deficiency in cardiac output occurs so rapidly and is of such intense degree that it is impossible to restore a relatively normal output by the above compensations Instead compensatory mechanisms are brought into play which redistribute the available low output in such a manner as to maintain an almost normal blood flow to vital organs at the expense of less important visceral and peripheral tissues In large measure the different clinical pictures associated with acute and chronic circulatory failure are due to the differences in compensatory processes as well as to differences in the severity and speed of development of an inadequate cardiac output

Shock, syncope and sudden death are forms of acute circulatory failure which differ in speed of onset of the circulatory failure and in severity and reversibility Sudden death occurs when the fall in cardiac output is so rapid and severe that vital medullary centers receive insufficient blood for survival Syncope denotes a very acute circulatory failure in which the available compensatory mechanisms cannot maintain an adequate blood flow to the brain, but as a rule the cerebral ischemia is transient and reversible In shock, the clinical picture develops rapidly but not as suddenly as in syncope Several hours usually elapse before the dynamic processes responsible for shock evolve the distinctive clinical phenomena Syncope and sudden death may also occur independently of acute circulatory failure

Shock syncope and sudden death are closely related in that one may merge into the other Transient attacks of syncope may be followed by one which is fatal Shock may occur with or without syncope

SHOCK

DEFINITION OF SHOCK

The term *shock* was originally applied to a clinical syndrome, is still recognized and diagnosed on the basis of clinical phenomena and should be defined in terms of these phenomena *Shock is a form of acute circulatory failure characterized by the rapid development of mental torpor and physical weakness, coldness of the extremities cold moist skin, rapid and weak pulse and a fall in arterial blood pressure* Unfortunately these criteria do not permit universal agreement as to the diagnosis in individual cases Generally, the diagnosis of shock is acceptable if there is hypotension below 80 mm Hg in association with the above clinical features Shock varies considerably with respect to severity and reversibility Hence it is often difficult to evaluate therapeutic agents

Shock is said to be *reversible* in the early stages when circulatory function may be restored by appropriate therapy Later there

develops a stage of *irreversible shock* which progresses to fatal insufficiency despite all therapeutic measures

Shock is sometimes used synonymously with peripheral circulatory insufficiency However the clinical syndrome and physiologic disturbances characterized as shock may be of cardiac or peripheral origin Furthermore since the circulation is an integral unit it is misleading to refer to a generalized circulatory insufficiency as peripheral

CLASSIFICATION OF SHOCK

Shock may be classified according to physiologic disturbances which result in a diminished volume flow of blood (cardiac output) These include (1) acute disturbances in (a) cardiac filling or (b) cardiac emptying which thereby sharply reduce the cardiac output, or (2) acute diminution in venous return due to a loss of blood plasma or intravascular water or to a pooling of blood in the small blood vessels

Shock is also classified according to the causative clinical conditions such as hemorrhagic shock traumatic shock burn shock etc These are incorporated in the following combined physiologic and clinical classification

Acute Circulatory Failure

- A Shock
- B Syncope (p 312)
- C Sudden death (p 316)

Shock

I Acute Deficiency in Venous Return
- A Deficient blood volume due to loss of blood or plasma
  1. Hemorrhagic
  2. Traumatic
  3. Surgical or postoperative
  4. Burn shock
- B Deficient blood volume due to dehydration and sodium depletion
  1. Vomiting and diarrhea (acute intestinal obstruction cholera acute diarrheas of infancy gastrointestinal external fistulae)
  2. Diabetic acidosis
  3. Addison s disease
  4. Heat exhaustion and syncope
- C Pooling of blood in small vessels (neurogenic? vasogenic? toxic? reflex? infectious?)
  1. Abdominal and testicular trauma
  2. Perforation of a hollow viscus
  3. Spinal anesthesia
  4. Acute pancreatic necrosis?
  5. Acute diffuse peritonitis?
  6. Acute febrile infections?
  7. Toxic forms of shock?

II Acute Deficiency in Cardiac Filling
- A Mechanical hindrance
  1. Sudden hemopericardium
  2. Acute pericardial effusions
- B Severe tachycardias with abbreviated diastole

III Acute Deficiency in Cardiac Emptying
- A Myocardial injury
  1. Acute myocardial infarction
  2. Rupture of valve cusp chorda papillary muscle or of septum
  3. Diphtheritic or rheumatic myocarditis (?)
- B Mechanical hindrance
  1. Massive pulmonary embolism
  2. Ball valve thrombus or tumor of left atrium
  3. Extreme mitral stenosis

PATHOLOGIC PHYSIOLOGY

Fundamental Mechanism[26, 158, 21, 27, 64, 103]

Despite the variety of clinical conditions and physiologic disturbances which may lead to shock there is a fundamental mechanism common to all which determines the clinical picture This common denominator is a rapid and severe *reduction in cardiac output with consequent tissue anoxia* Secondary (compensatory?) consequences of the reduction in cardiac output also contribute to the production of clinical manifestations

Shock is a dynamic process and its physiologic abnormalities may be considered in three stages (1) initial disturbances (2) compensatory mechanisms (3) stage of irreversible shock

1 *Initial Disturbances.* Like chronic circulatory failure acute circulatory failure begins with an inability of the heart to maintain an adequate output of blood[105, 3, 174] This may be caused by a reduction in blood volume and consequent diminution in venous return to the heart or it may be due to some cardiac or extracardiac disease which prevents the heart from filling or emptying properly

The low cardiac output may be denoted clinically by the mental and physical weakness low metabolism and occasional sub-

normal temperature The weakness of the pulse *and a low pulse pressure may be evi* dence of an extremely small stroke output The tachycardia, usually present is a well known cardiac compensation for a diminished stroke volume Actual measurements have disclosed early and sharp reduction of cardiac output in experimental shock [105, 167] By means of intracardiac catheterization and the use of the Fick principle Cournand and his associates[32] determined the cardiac output in clinical cases of shock due to skeletal trauma hemorrhage or burns Regardless of the type of injury they found the essential circulatory abnormality in these cases of shock to be a reduction in the cardiac output averaging about 35 *per cent* The right atrial and systemic venous pressure are diminished The circulation time is prolonged as determined with the aid of radioactive red cells or dyes in *animals with experimental shock* [203, 166] *The* delay appears to be in the systemic vessels since the pulmonary circulation time was found to be normal

2 Compensatory Mechanisms The sudden and severe fall in cardiac output is a threat to all tissues but especially to the brain which is most sensitive to anoxia and to the heart which is also vital for survival It is essential that the reduced volume flow available be redistributed in favor of the brain and heart and at the expense of the peripheral tissues and splanchnic viscera [6, 4] Moreover an adequate blood pressure must be maintained in order to perfuse these vital organs Both objectives can be and are accomplished by widespread vasoconstriction Because of the relatively *poor vasomotor innervation of the cerebral* and coronary arteries, their blood flow is relatively little affected by the generalized vasoconstrictor mechanism On the other hand vasoconstriction in the skin and splanchnic vessels so increases the peripheral resistance that blood pressure is maintained at much higher levels than would otherwise be possible with the diminished cardiac output

In contrast with chronic circulatory failure (congestive heart failure) vasoconstriction and redistribution of blood flow are the major compensations for shock, a compensatory increase in *blood volume may occur but is of* negligible significance In chronic circulatory failure, there is adequate time to increase the blood volume, which tends to restore a relatively normal output in the early stages, *vasoconstriction also occurs but is of* secondary importance

The occurrence of widespread vasoconstriction and redistribution of blood in shock has been demonstrated by many clinical and experimental observations [11, 14]

Perhaps the most striking evidence of intense vasoconstriction is found in the skin, which is extremely cold and moist, especially in the distal parts of the circulation such as the extremities and tips of the nose Baldes and associates[10] found that when shock was induced in dogs by intestinal manipulation there was as much as 75 per cent reduction in blood flow through the femoral artery even though the blood pressure was maintained at normal levels Similar evidence of disproportionate vasoconstriction may be found in the experiments of Erlanger, Gesell and Gasser [■] *who observed a 60 per cent reduction in the* blood flow through the salivary gland, following only a 10 per cent reduction in circulating blood volume without change in arterial pressure *In clinical cases of surgical shock Free*man, Shaw and Snyder [75] with the aid of the venous occlusion plethysmograph, observed a striking diminution in blood flow through the hand and a loss of the normal ability to increase this flow by warming or by applying and releasing a tourniquet The fact that the blood flow (cardiac output) in experimental and clinical shock generally declines before the blood pressure falls, also indicates the early development of vasoconstriction [105, 91, 161]

Of special interest are the findings that in the early phase of shock there is a decline in *renal blood flow which is even greater* than the decline in cardiac output [113, 161, 198] Thus while the total blood flow decreases to about half of normal the renal blood flow, which is normally 20 to 25 per cent of the total is reduced to one tenth or less of its usual amount [113]

The existence and significance of renal shunts[197] through the renal medulla in cases of shock is undetermined Apparently, in acute as in chronic circulatory failure, the kidneys play an important role in the defense of the organism either in restoration of cardiac output by retention of sodium and water and thereby increasing the blood volume and venous return, or by a vasoconstrictive redistribution of an inadequate blood flow and maintenance of blood pressure

The mechanisms by which vasoconstriction redistribution of blood and maintenance of blood pressure are effected are probably multiple The role of the adrenal medulla and sympathetic nervous system is best known That sympathetic vasoconstriction is important in producing the shock syndrome is denoted by the cold sweat in human cases and by the difficulty in producing experimental shock after bilateral sympathectomy [7] There is also evidence that reflexes by way of the carotid sinus and vasomotor center adrenal cortical hormones [77] and renin like or other pressor substances released from the kidney in response to ischemia[33, 184] participate in the compensations for acute circulatory failure

At the same time that these vasoconstrictive phenomena are occurring in various organs and tissues during the compensatory stage of shock the blood pressure may decline but is still adequate for cerebral and coronary blood flow There may be mental apathy but consciousness and coherence are usual There is no clinical or electrocardiographic evidence of significant cardiac damage or of an inability of the heart to handle the venous return [211]

3 *Stage of Irreversible Shock.* Prolonged severe shock eventually leads to failure of these compensatory mechanisms, with consequent progressive decline in cardiac output and blood pressure profound tissue anoxia involving also the heart and brain and death During the uncompensated or irreversible stage of shock restoration of blood volume and other therapeutic measures which are usually effective in the early stages are incapable of altering this baneful series of events

During the stage of irreversible shock the continued fall in cardiac output and in blood pressure occurs even when there is no significant further reduction in blood volume The circulation time becomes greatly prolonged These findings suggest that the decline in cardiac output in this stage is due to peripheral stasis and the inability to build an adequate blood pressure is due both to the failing output and the failure to maintain compensatory vasoconstriction In other words irreversible shock is associated with a reduction in peripheral resistance and a pooling of blood in small vessels

These concepts are supported by direct observations of capillaries in various animals with induced shock In the compensated stage there is accentuated vasoconstrictor activity of metarterioles and precapillary sphincters and hyperreactivity to small doses of epinephrine In the irreversible stage there is a diminution in vasomotor activity with dilatation of arterioles and venules diminution or absence of response to epinephrine capillary stagnation and eventual cessation of blood flow [270, 31, 115] Postmortem observations have disclosed generalized capillary dilatation and stasis and packing with erythrocytes Studies of blood volume in experimental shock with radioactive isotopes disclosed evidence of widespread 'trapping' of red cells within the minute vessels of all the organs of the body [80] Thus in the irreversible stage of shock pooling of blood in atonic small vessels intensifies the previous deficiency in venous return and cardiac output and nullifies the compensatory mechanisms which maintained a sufficient blood pressure and blood flow to vital organs However these secondary and terminal occurrences should not be confused with the initiating causes of shock

The actual cause of irreversibility of shock is uncertain Metabolic or toxic changes induced in the organs which suffered from prolonged and intense vasoconstrictive anoxia during the compensated period of shock are the most probable factors inducing irreversible shock The importance of compensatory vasoconstriction in causing irreversible shock is supported by the observation that the occurrence of irreversible hemorrhagic shock in experimental animals was delayed and its incidence diminished when dibenamine a sympatholytic drug was administered twenty hours before the shock producing venesection [214] The mortality from hemorrhagic and other forms of shock in rats was largely prevented by pretreatment with dibenamine [8] The vascular atony and capillary stasis and trapping of blood may be due to the direct or indirect effects of prolonged vasoconstriction and tissue anoxia

Of the organs suffering from vasoconstriction the *liver* is most sensitive to anoxia perhaps because of the relatively low normal oxygen content in the portal vein its chief source of supply There is considerable evidence of hepatic dysfunction in shock as denoted by the rise in blood amino nitrogen[30, 178] and other chemical changes (p 309) Further evidence of the role of liver damage in irreversible shock is seen in the observation that

irreversibility of hemorrhagic shock in dogs can be prevented by via perfusion of the liver (by way of the splenic vein) with normal donor's blood.[69, 205] Similar arterial transfusion into the jugular vein of the shocked animals was ineffective. Ligation of the dog's inferior vena cava above the liver produced prompt shock, which could not be reversed by infusing any amount of whole blood or saline solution.[64] Shorr and his associates[184] reported the finding of a humoral substance ("vasodepressor material"—VDM identified as the iron-containing protein ferritin) elaborated essentially by skeletal muscles and liver after prolonged shock and responsible for the atony and stasis found in small blood vessels in the irreversible stage. On the other hand, a direct relation of ferritin (VDM) to shock is improbable since it was incapable of inducing shock in dogs when injected intravenously in large doses, even after the liver and kidneys were removed.[67, 182]

The *kidney* has been mentioned as suffering from intense vasoconstriction and reduction in blood flow during the compensated stage of shock. This may lead to organic renal changes, especially in the tubules, if shock is severe and prolonged (lower nephron nephrosis[199, 200]). Oliguria or anuria, urine of low specific gravity, low urea clearance and uremia may result. Such renal failure may develop as a result of prolonged anoxemia and organic changes even after normal circulatory function has been reestablished, as in the so-called crush syndrome (p. 953). Renal failure may contribute to the acidosis of shock and may itself be responsible for death. But it is unlikely that renal anoxia is responsible for the irreversible stage of shock.

Anoxia of the *skeletal muscles* during prolonged shock gives rise to metabolic disturbances which contribute to the alterations in blood chemical findings (p. 309).[43] But the possible role of these disturbances in irreversible shock is uncertain.

The *heart* itself, which is fairly well supplied with blood during the compensated stage, may suffer if shock is severe and prolonged.[211] Depression in myocardial function may thereby contribute to the circulatory debacle that occurs during irreversible shock. Wiggers and Werle[213] showed that the capacity of the ventricles to respond to progressive increments of filling (venous) pressure was reduced in animals with hemorrhagic shock. Kohlstaedt and Page[118] observed a stage of cardiac constriction followed by one of cardiac dilatation corresponding to similar peripheral vascular changes in progressive shock. Prinzmetal and Bergman[164] observed a maximal increase in the number of open capillaries in the hearts of rats with burn shock and concluded that the heart in shock suffers from decreased coronary flow, capillary atony with retention of metabolites and myocardial dehydration. Other studies indicate that there is myocardial ischemia from diminished coronary flow in experimental hemorrhagic shock and that there are consequent metabolic changes in heart muscle, such as a destruction of cocarboxylase.[43] A sharp reduction in the normally high myocardial extraction coefficient of pyruvate has been noted, as well as relative myocardial oxygen deficiency.[69] Opdyke and Foreman[154] reported experimental evidence that although the coronary blood flow may be reduced in shock, it is adequate in terms of the diminished work of the heart. On the other hand, Sarnoff and associates[177] noted myocardial failure with a rise in left and right atrial pressures as a complicating factor in experimental hemorrhagic shock. These observations indicated that deficient coronary blood flow contributed to the myocardial failure. In cases of clinical shock, e.g., after acute hemorrhage or massive pulmonary embolism, we have observed myocardial necrosis or infarction without coronary occlusion, due undoubtedly to functional coronary insufficiency.[79] Despite these evidences of late myocardial damage in severe shock, it is probable that they are the consequences and not the cause of irreversible shock.

The *cerebral blood flow* is diminished during shock, but cerebral metabolism may be normal or diminished and oxygen extraction increased or reduced.[63, 6a] Apparently, cerebral metabolism may be maintained at normal levels in some cases despite diminished cerebral blood flow.

ETIOLOGY AND PATHOGENESIS

Bacterial Infection

Various studies in experimental animals have implicated intestinal bacteria as responsible agents in irreversible shock.[61] When shock was produced by bleeding, dogs to which antibiotics had been first administered experienced a lower mortality rate and greater tolerance to the hypotension than dogs which

had not received antibiotics Furthermore in the dogs with antibiotics rapid recovery could be effected by restoration of the full volume of blood when shock was irreversible in the control animals A lethal factor was obtained from the livers of dogs in irreversible hemorrhagic shock and this factor was found to depend on bacterial action during the state of shock[170] On the other hand Nelson and Noyes[147] found an almost identical incidence of positive blood cultures of Clostridium perfringens and Corynebacterium in control dogs and dogs in terminal hemorrhagic shock But whether or not such bacteria contribute to irreversible shock in the dog the applicability of such a mechanism to the human is improbable partly because of the significant difference in bacterial flora in the dog and the human

Acute Deficiency in Venous Return Caused by Loss of Blood or Plasma Volume[3, 26, 212, 44]

Under this heading are included cases of shock due to hemorrhage trauma burns surgery etc in which the initiating cause is a reduction in circulating blood volume Harrison[86] refers to this group as hematogenic shock and Fishberg[62] terms it oligemic shock The reduction in circulating blood volume results in a diminution in the venous return and consequently in a decline in cardiac output Diminished venous return is denoted in clinical shock by the collapsed superficial veins and by the finding of very low atrial pressures by cardiac catheterization[3] A progressive increase in the circulation time[203] indicates that slowing of blood flow later accentuates the decline in venous return

The classic studies of Robertson and Bock[170] and of Keith[111] during World War I disclosed striking reductions in circulating blood volume in cases of traumatic or wound shock and a definite relationship between the reduction in blood volume and the severity of shock Numerous other experimental and clinical studies have demonstrated the close causal relationship between reduction in blood volume and the development of hemorrhagic traumatic and burn shock Studies of traumatic shock in dogs revealed that the clinical picture of shock appeared when there was at least a 30 per cent reduction in blood volume and in dogs that succumbed the reduction was 40 per cent or more[87] In clinical studies of traumatic shock similar pronounced declines in circulating blood volume (30 to 40 per cent below normal) were discovered with the aid of the blue dye T 1824[3, 131] Practically this denotes that clinical shock follows the rapid loss of about 1 5 to 2 0 liters of blood Similar reductions in blood volume occur in burn shock[119] The latter usually develops when more than 10 per cent of the cutaneous surface is involved

Theories of Reduction in Blood Volume

Local Fluid Loss The cause of the reduction in blood volume is usually clear when there is massive external bleeding In surgical or postoperative shock the amount of blood loss during operation is much greater than was formerly recognized Preoperative and postoperative vomiting or bleeding and loss of fluids from excessive perspiration are factors contributing to the reduction in blood volume

In recent years it has become increasingly manifest that gross reductions in blood volume in cases of wound skeletal and burn shock may be due entirely or almost entirely to the extravasation of blood or plasma out of the blood stream and into the injured area When shock was induced in animals by trauma to a hind leg comparative weights of the injured and normal legs disclosed that the loss of blood and plasma into the injured leg was sufficiently large to account for the reduction in blood volume and occurrence of shock[13] Similarly shock induced experimentally by intestinal manipulation or by burns could be explained by the local loss of fluid in the burned or damaged tissues[77, 81] These findings have been confirmed by Nickerson[149] and by Ashworth et al[7] who demonstrated quantitatively that the fluid loss was equal to the observed reduction in circulating blood volume Of interest also in this connection are the observations of Duncan and Blalock[40] that shock does not develop if local fluid loss after trauma is prevented e g by application of a cast In certain forms of experimental burn shock there is a diminished circulating blood volume but little or no evidence of fluid loss since capillary atony and visceral congestion are prominent the shock has been attributed to capillary stasis due to a toxic humoral factor and consequent reduction in venous return[144]

Toxic Factors The production of circulatory failure with a fall in blood pressure and reduction in blood volume following the injection of histamine[31] suggested that toxic

substances liberated by injured tissues might be responsible for shock. Shock has been produced by a variety of extracts of normal and traumatized tissues but the results are not consistent and the type of shock induced differs in fundamental respects from traumatic shock.[11, 138, 113] Similarly cross circulation experiments in which the production of shock was attempted by transfusion of blood from shocked to normal dogs have usually been unsuccessful or insufficiently controlled.[13, 83] Although infection may be a complicating factor in some cases of traumatic shock,[61] it is neither a usual nor a fundamental cause of the shock syndrome.

Several variants of the toxic theory of shock have been recently proposed. It has been shown that, at least in experimental traumatic shock, bacterial toxins may be important, especially the toxins of clostridia.[166] The reported appearance of a vasodepressor material from shocked liver and skeletal muscle has been mentioned.[164] Profound metabolic changes with alteration of the chemical pattern of the blood have been reported,[43] but these are secondary factors which may enhance the progress of shock and lead to irreversibility, but do not initiate the disorder. Retention of potassium with hyperpotassemia may occasionally be a contributing factor in causing death,[16] but is not of primary importance in the etiology of shock. The *adrenal cortex* participates in the metabolic reactions to shock, but is not the cause of traumatic shock or of its irreversibility.[49, 96]

Nervous factors have been invoked as the possible cause of shock, but the weight of evidence is strongly opposed to the concept that traumatic shock of the type under discussion is induced by nervous reflexes.[160] The occurrence of so-called primary or neurogenic shock is discussed below.

The theory of generalized capillary permeability with leakage of fluid from the circulation, as contrasted with local extravasation in the injured area, has been championed most vigorously by Moon.[138] This was based essentially on (1) pathologic findings in shock which represent terminal changes, (2) analogy with the findings in histamine shock which differs fundamentally from traumatic shock, and (3) an exaggerated emphasis upon hemoconcentration of blood, which has recently been shown to be absent except in shock due to burns or abdominal injuries with peritonitis.[31] On the other hand, there is adequate evidence that the reduction in blood volume can be explained by local fluid loss[13]; studies with radioactive sodium show a decrease in transcapillary exchange instead of the increase to be anticipated if capillary permeability were enhanced[79], and a study of radioactive proteins in hemorrhagic and tourniquet shock[67] and of radioactive dyes in burn shock[29] discloses no evidence of generalized capillary leakage. The theory of generalized capillary leakage no longer appears tenable.

Acute Deficiency in Blood Volume and Venous Return Due to Dehydration

In this etiologic type of shock, a deficient venous return and cardiac output are likewise due to a reduction in circulating blood volume, the latter is caused, not by a loss of blood or plasma, but by an excessive loss of fluid and electrolytes by way of the kidney, gastrointestinal tract or skin. This type of shock is sometimes termed "medical shock."[4] Because the loss of blood volume is due to or concomitant with a loss of sodium, the clinical picture of shock is complicated or overshadowed by the effects of loss of base (acidosis) and tissue dehydration.

In the intense *gastroenteritis* of infancy, in *cholera* and in *high intestinal obstruction* with vomiting, the excessive loss of fluid is obvious, while oral replacement is either impossible or grossly inadequate. With vomiting there is chiefly loss of chlorides with some sodium, and with diarrhea chiefly a loss of sodium. Since the extracellular water content is essentially a function of dissolved electrolytes, such loss of ions is associated with a reduction in circulating blood volume. Actual diminution of blood volume due to diarrheas of infancy has been noted.[35, 133]

In *diabetic acidosis*, there is an excessive loss of sodium through the kidneys, both as sodium chloride and in combination with ketone radicles.[7] This results in an excessive loss of fluids which are not replaced because of nausea or vomiting, and consequently in a reduction of blood volume and shock.[159]

In *Addison's disease*, deficiency of the sodium regulating factor of the adrenal cortex leads to excessive renal excretion of sodium, a corresponding loss of fluid and a reduction in circulating blood volume.[172] The fluid loss is often intensified by diarrhea and vomiting which occur during crises. The clinical picture

of shock in Addison's disease is complicated not only by dehydration but by disturbance in carbohydrate metabolism by retention of potassium and by fever and sensitivity to mild infections

Acute Deficiency in Venous Return Due to Pooling of Blood in Small Vessels

A deficiency in venous return and in cardiac output with a consequent clinical picture of shock can result from pooling or stagnation of blood in small vessels and without any external loss of blood or plasma Such pooling may result from direct impairment of vascular tone with consequent vasodilatation (vasogenic shock of Harrison[85]) or from reflex or neurogenic vasodilatation (neurogenic shock)

The former is represented by *histamine shock* and perhaps various types of chemical toxic or anaphylactic shock The neurogenic type of shock is represented by the almost immediate collapse which follows a bullet wound abdominal blow (solar plexus punch) testicular injury or perforation of a hollow viscus This type of shock is also classified as primary shock because of its early onset after trauma as compared with the secondary shock or wound shock which we have been discussing and which usually develops after several hours Syncope (p 312) is common in this neurogenic type of shock

This form of shock differs from the previous groups also in that a fall in arterial blood pressure (due to vasodilatation) precedes the decline in cardiac output This was observed particularly in the shock following experimental spinal anesthesia[19] According to the observations of Smith and collaborators[185] the relaxation involves the postarteriolar vessels i e the capillaries and small venules

There is uncertainty as to the mechanism of shock in such conditions as acute pancreatic necrosis large peripheral embolism acute diffuse peritonitis and acute infections[4, 98, 71] Direct or reflex vasodilatation due to toxic substances reflex vasodilatation due to neurogenic impulses and in some cases also local extravasation of fluid and dehydration may be concerned Gilbert and associates[81] found that the hypotension in 5 patients with shock due to infection was associated with a normal cardiac index and a low total peripheral resistance Norepinephrine administration was followed by a rise in arterial pressure without increase in cardiac output

Acute Deficiency in Cardiac Filling

This group comprises cases of shock due to the sudden development of inflammatory pericardial effusion or hemopericardium which compresses the heart and prevents its filling (cardiac tamponade) Occasionally the sudden development of an extreme tachycardia likewise prevents cardiac filling by abbreviating diastole In this group there is often a simultaneous initial pooling of blood proximal (upstream) to the right chambers of the heart i e in the systemic circulation Incomplete filling causes a sharp drop in cardiac output and shock or syncope[11]

A more detailed discussion of acute cardiac tamponade can be found on page 593 and of tachycardias on page 347

Acute Deficiency in Cardiac Emptying

There is a primary reduction in cardiac output in these cases either because of some mechanical obstruction (ball valve thrombus massive pulmonary embolism) or because of sudden impairment of cardiac function (acute myocardial infarction) This type of acute circulatory failure is sometimes termed cardiac shock or cardiogenic shock The clinical picture is essentially identical with that of shock due to an acute reduction in venous return The circulation time is usually prolonged but there are scanty data as to the blood volume

In cases of shock due to acute myocardial infarction there is a tendency to pooling of blood proximal (upstream) to the left cardiac chambers This often results in acute pulmonary congestion (left ventricular failure) in association with shock When acute myocardial infarction occurs in a previously insufficient heart there may be a combined picture of congestive heart failure and shock In contrast with the tendency to elevated blood volume in congestive heart failure the blood volume is usually somewhat reduced in cases of shock due to acute myocardial infarction[1]

The individual conditions responsible for this etiologic type of shock are discussed elsewhere under their respective headings

PATHOLOGY OF SHOCK

Since shock represents a dynamic progression of physiologic abnormalities the reported pathologic findings in experimental and clinical shock must be viewed as terminal changes in fatal cases

During abdominal operations on patients in shock the viscera and peritoneum are often found to be remarkably pale.[1] On the other hand Gasser Erlanger and Meek[78] observed great dilatation of capillaries and venules, packed with red blood cells, in various types of experimental shock. More recently Moon and Kennedy[140] and Moon[133] have especially emphasized the occurrence of diffuse capillary congestion, edema, effusions and petechial hemorrhages in the viscera following experimental and clinical shock.

Gastric and intestinal ulcers have been repeatedly observed in cases of shock due to histamine following adrenalectomy due to burns [?] and in patients who succumbed after major operative procedures or diseases associated with shock.[157] The pathologic findings in the latter group were interpreted as the result of intense vasoconstriction.[114]

There may be fat vacuoles in myocardial fibers in the central cells of the liver lobules and in the ascending loop of Henle in the kidney,[1,6] depletion of lipid in the adrenal cortex,[15] pulmonary fat embolism [228] and central necrosis of the liver.[48] Cerebral and coronary infarction may be precipitated by shock.

CLINICAL FEATURES OF SHOCK

General Appearance and Behavior[94]

The patient may be restless or he may lie quietly, apathetic and oblivious of his surroundings. Restlessness is common in the early stages of acute hemorrhage. Occasionally the patient in shock is able to drive himself home or to a physician's office or he walks into a hospital emergency room. Occasionally he is found wandering aimlessly about the scene of his injury.

More often the patient is extremely weak and incapable of any but the mildest physical exertion. Mental torpor corresponds with his physical lethargy. His responses are feeble and hesitant but usually coherent. Advancing shock is characterized by progressive physical and mental exhaustion bordering on coma. Sensation is dulled and responses become incoherent or absent.

The Skin

The skin is *pale and cold*. In very severe shock the pale skin is mottled bluish red (cutis marmorata) owing to irregular congestion and constriction of superficial blood vessels. The coldness and pallor of the skin are most pronounced in the hands, feet and tip of the nose. Occasionally, as in shock due to a ball valve thrombus or extreme mitral stenosis, I have seen intense cyanosis with foci of necrosis in these peripheral regions. The skin temperature may be low even when the patient is febrile.

A grayish cyanosis is frequent. *Excessive perspiration* renders the skin clammy as well as cold.

The *rectal temperature* may be subnormal due to a low rate of metabolism and loss of heat through perspiration.

The Pulse

A rapid weak pulse is characteristic. Terminally there may be a bradycardia. A rapid pulse usually appears before the decline in blood pressure and may be of diagnostic value.

The Respiration

This is variable according to the etiologic factor. Often it is deep and rapid due to increasing acidosis.

The Blood Pressure

Hypotension is characteristic of shock but the blood pressure may remain normal at the onset of shock when a significant decline in cardiac output has already occurred.[10] The compensatory vasoconstriction occasionally is so intense that the blood pressure is temporarily above normal.[116] However, a progressive decline in blood pressure is the rule. Usually the blood pressure is below 90 mm Hg and in very severe and in irreversible shock below 70. The *pulse pressure* is reduced.

The Heart

In the cases of shock due to a deficient venous return there is no overt evidence of cardiac impairment. Evidence of myocardial depression in advanced experimental shock has been discussed.

The Veins

The superficial veins are collapsed. The difficulty of inserting a needle is well known. The venous pressure is low (1 to 2 cm) and cardiac catheterization has disclosed that the right atrial pressure is likewise low.[22]

The Urine

The urinary output is diminished and in severe shock there may be complete anuria (p 953). Renal clearance studies show a depression of renal blood flow and of glomerular filtration. Despite a low urinary output the specific gravity may be low.

The Blood

A leukocytosis is common, especially in

hemorrhagic shock, but leukopenia may be present in severe shock.[21] A depression of circulating eosinophils is evidence of adrenocorticoid response to injury.[55, 56]

Hemoconcentration is usual in shock due to burns, to dehydration and in some cases of abdominal injuries. *Hemodilution* is observed in shock due to hemorrhage, skeletal trauma and crushing wounds.[22]

Hyperglycemia occurs early and is believed to result from a compensatory secretion of epinephrine.

Acidosis[21] is usual in well developed shock. It is due to an accumulation of lactic, phosphoric and pyruvic acids in the blood. Lactic and pyruvic acids increase because of excessive production in the skeletal muscles and because of impairment of liver function.[10] The increase in phosphates is due chiefly to impaired renal excretion. The accumulation of fixed acids releases bicarbonate which is eliminated as carbon dioxide through the respiratory tract. A diminution in alkaline reserve, denoted by a low carbon dioxide combining power, results from loss of sodium excreted in combination with the fixed acids. The pH of the blood may be significantly diminished but is usually relatively normal.

Urea and nonprotein nitrogen are elevated because of increased catabolism and deficient renal excretion.[3]

An *elevation of alpha amino nitrogen* results from increased catabolism and impaired deamination by the liver.[176] Elevation of arterial blood ammonia occurs in experimental oligemic shock and aggravates the clinical picture.[148]

The *arterial oxygen* is usually normal until preterminally. The *venous oxygen content* falls progressively.[167] The *arteriovenous oxygen difference* is increased. This is indicative of a prolonged circulation time which compensates for the low cardiac output by permitting a more complete oxygen extraction by the tissues.

Potassium may be increased because of increased protein catabolism, impaired renal excretion, or adrenal cortical deficiency.[165]

TREATMENT OF SHOCK

Prophylaxis

Many types of shock are easily preventable. In *surgical procedures* preoperative correction of dehydration and anemia, omission of drastic purgation, restoration of glycogen reserves in the liver, elimination of excessive sweating, careful hemostasis and minimal handling of tissues during the operation, expert administration of anesthesia and avoidance of long operations will minimize the incidence of postoperative shock. Traumatic shock may be avoided by prompt control of bleeding with the aid of pressure, ligature (or tourniquet, if necessary) and especially by rapid transportation to a hospital where more definitive measures can be carried out. Protection from cold and pain and the rapid splinting of injured parts are also valuable prophylactic measures.

Early Treatment

Successful treatment of shock must begin early, before the irreversible stage is reached. This means early diagnosis. The probability of shock should be gauged from the severity of trauma, the extent of a burn, outward evidences of bleeding, the nature of an operation or of other circumstances associated with the causative condition. If these circumstances suggest that shock is probable, treatment should be instituted before there are frank clinical evidences of shock.

Treatment

The *causative condition* should be corrected. This may mean the ligation of bleeding vessels, débridement of destroyed tissues, maintenance of a free respiratory airway, setting of fractures, closure of a perforated viscus, drainage of a pericardial effusion, removal of an atrial tumor, administration of adrenal cortical extract and sodium in Addison's disease, or of insulin in diabetic acidosis. In traumatic shock the patient should be kept supine or with the foot of the bed or stretcher elevated, except when there is a severe head injury, pulmonary edema or a chest wound associated with respiratory distress. Body warmth should be conserved but overheating should be avoided and the danger of burns should be remembered. Morphine or other narcotics or sedatives should be given only as needed to relieve pain or allay anxiety, overdosage being strictly avoided.

Transfusion of whole blood is the mainstay of treatment in shock due to hemorrhage or trauma.[19, 167] It has also been recommended in the treatment of burns.[84] Blood should be given *early* and in adequate amounts. The latter can be gauged by observation of the clinical response and determinations of the

blood count, hematocrit and blood volume In the presence of shock, recovery usually requires at least 1000 to 1500 cc of blood Arterial (radial or aortic) transfusion has been recommended in very severe cases of shock [116] Arterial transfusion[201, 31] may be preferable to intravenous transfusion in shock associated with cardiac arrest during complete heart failure surgery or mitral stenosis and possibly in cases of shock due to myocardial infarction *The arterial transfusion is designed* to raise aortic pressure and perfuse the coronary vessels without requiring cardiac activity On the other hand there is evidence that in hemorrhagic and traumatic shock transfusion of blood via an artery is no more effective than intravenous transfusion [2, 186] with respect to raising the arterial pressure and increasing the coronary blood flow The rate of infusion of blood may be more important than the route by which it is administered [127] Care should be taken to avoid the precipitation of pulmonary edema by too rapid or excessive transfusions (or infusions of plasma or saline) especially in elderly individuals and in those with known cardiac disease In cases of shock with extreme oliguria or anuria the parenteral administration of fluids must be given with particular caution because of the hazard of congestive heart failure Proper cross matching of blood with respect to type and Rh factor is essential

Plasma and other blood substitutes (plasma expanders) including human albumin, dextran polyvinyl pyrrolidone (PVP) and gelatins are relatively much less satisfactory in hemorrhagic traumatic or surgical shock Such blood substitutes are indicated in the early stages of burn shock in which there is relatively little loss of erythrocytes and the hematocrit is elevated [47] As a rough guide, 75 cc of plasma or plasma expanders are given in the first 24 hours for each per cent of body surface burned and somewhat less on the second day Thereafter the amount is gauged by the clinical condition *of the patient, and* by determinations of blood counts hematocrit specific gravity and chemical examinations of the blood [91, 5, 3] The danger of viral hepatitis is a serious disadvantage of plasma Fluid and electrolytes are given parenterally or orally to supplement the plasma Good results have been reported in the treatment of burn shock with very large amounts of sodium lactate [85]

Plasma Expanders [83, 94] This term refers substances of relatively high molecular weight which, when infused into the blood stream, remain long enough to augment the volume of circulating fluid by increasing the oncotic pressure These substances should be non toxic relatively inexpensive and not retained in the body indefinitely Three of the recently studied plasma expanders are dextran, polyvinyl pyrrolidone (PVP) and oxypoly gelatin (OPG) *The plasma expanders*, especially dextran, possess the advantage of a lower incidence of reactions than after blood or plasma, especially with regard to the occurrence of homologous serum jaundice

Dextran, which is a polydispersoid glycose polymer with a molecular weight conforming to that of albumin (about 100 000),[198, 106, 94] has recently been recommended and fairly widely used in Sweden as a plasma substitute for the prevention and treatment of surgical and other forms of shock Dextran is formed by the action of the bacteria Leuconostoc mesenteroides on sucrose It is not pyrogenic or toxic but some individuals experience allergic reactions [108] Prolongation of bleeding time and hemorrhagic tendencies may be observed among patients who have received large amounts of dextran according to Jaenike and Waterhouse [104] but no such bleeding tendency was noted by Artz et al [3] Most of it is removed slowly from the blood stream in four to seven days [18] Studies in dogs[105] of dextran labelled with radioactive carbon (C^{14}) disclosed rapid excretion of those fractions of dextran with a low molecular weight whereas the fractions of higher molecular weight were retained in *the body for longer periods* A high concentration of dextran (C^{14} activity) was found in the liver and lymph nodes and uniform distribution in other tissues Unlike most of the other plasma substitutes, dextran is normally metabolized [97] In cases of shock it is said to produce a prompt and lasting increase in blood pressure [200] It has been administered *intravenously as a 6 per cent dextran solution* in 0 9 per cent sodium chloride In surgical cases and combat casualties 500 to 1500 cc is usually employed [2, 70] Where there is marked loss of blood it should be replaced by blood alone But if there is only slight loss of blood dextran may be used to combat shock or a transfusion may be given followed by 500 cc of dextran Or dextran may be given first if there is a delay in obtaining appropriate blood

Studies in normotensive dogs[60] and in humans[5] indicate that dextran is a more effective plasma expander than either of the more recently introduced polymers PVP or OPG.[60] Other studies indicate that dextran produces striking increments in blood volume when administered to both normovolemic and oligemic (bled) human subjects, especially the latter.[90] The administration of 500 cc. of a 6 per cent solution of dextran was found to increase the blood volume by 960 to 2850 cc. (average 1880 cc.), the maximal increase occurring between one quarter hour and 6¼ hours after the infusion.[195]

Polyvinyl pyrrolidone (PVP)[167, 1, 120] This is a synthetic, water-soluble, hydrophilic polymer of heterogeneous molecular size with an average molecular weight between 35,000 and 40,000. It is administered intravenously in a 3.5 per cent solution in buffered physiologic saline which is virtually isotonic with normal plasma. Usually 500 to 1000 cc. is given to prevent or combat surgical shock. It was used successfully in Germany during and after World War II and has since been reported to be effective in obstetrical,[19] burn, traumatic[14] and hemorrhagic shock.[20] Its excretion resembles that of dextran, but its plasma levels are usually lower and it is somewhat less effective. Unlike dextran it is not metabolized, 40 to 50 per cent being stored and subsequently eliminated very slowly in a period of weeks or months.[22] The particles of largest molecular weight (above 120,000) are retained for years in the reticuloendothelial system.

Oxypolygelatin (OPG) is a gelatin polymer which may be administered intravenously in a 5 per cent solution in physiologic saline.[4, 83] Some batches of OPG are superior to PVP but in general OPG is less effective as a plasma expander than dextran.[89] There is a larger unaccounted loss of OPG following intravenous infusion than of either dextran or PVP.[89, 5]

Crystalloid solutions, especially an isotonic (0.85 per cent) solution of sodium chloride or other sodium-containing solutions, are given intravenously or subcutaneously until blood and plasma are obtained, to supplement plasma in burn shock, and in the treatment of shock due to dehydration. Potassium salts may be necessary in the dehydration diarrhea of infants.[82]

Vasoconstrictor (pressor, sympathomimetic) drugs[164, 74, 210, 137] have been more widely used in recent years in the treatment of all forms of shock, but are only of transient and secondary value when shock is due to blood loss. Their use is based on the premise that sympathetic vasoconstriction in shock is incomplete and that the dangerously low blood pressure of shock may be elevated by further vasoconstriction. The advantages of raising the blood pressure to maintain an adequate cerebral and coronary blood flow and glomerular filtration are regarded as outweighing the possible risks of further constriction of the peripheral and splanchnic vessels.

Norepinephrine (Levophed), Wyamine (mephentermine) sulfate, methoxamine (Vasoxyl), Neo-synephrine and metaraminol (Aramine) administered intravenously or intramuscularly have been used most frequently. They are discussed in connection with the treatment of shock in acute myocardial infarction (p. 562). Paredrine (10 to 20 mg. intramuscularly or 5 to 10 mg. intravenously) and Neo-synephrine (5 mg. subcutaneously) are useful in the shock which may follow spinal anesthesia.

Alkalis in the form of a 5 per cent solution of sodium bicarbonate or a $^1/_6$ molar lactate solution may be given to correct the acidosis associated with shock. About 60 cc. of the $^1/_6$ molar lactate per kilogram body weight increases the CO_2 combining power of the blood 25 to 35 volumes per 100 cc.

Oxygen is of doubtful value in most cases of shock since the arterial oxygen is normal. It is useful in cases with pulmonary injuries or complications and in cases of burns with exposure to noxious fumes.

Digitalis is not indicated for the treatment of shock.

Adrenal cortical hormone has been reported to be useful in the prevention of experimental shock and the treatment of clinical shock,[155, 13, 150] but more recent studies have disclosed no benefit from cortisone or ACTH in experimental hemorrhagic shock.[100, 68] On the other hand, shock appearing suddenly during anesthesia or operation has been attributed to the preoperative discontinuation of ACTH or cortisone in patients who had been previously treated with these steroid hormones.[14] The preoperative and postoperative administration of these hormones has been recommended to avoid shock in such patients.[14] There is experimental evidence suggesting that the effectiveness of nor-

epinephrine is dependent on an adequate supply of adrenal corticohormone Potentiation of norepinephrine by adrenocortical steroid hormones was reported in patients in whom adrenal insufficiency due to prolonged shock and myocardial infarction caused failure of response to vasopressor drugs [128] Occasionally these steroid hormones are life saving in shock associated with the toxemia and high fever of bacteremias until antibiotics control the causative infection Cures of the Waterhouse Friderichsen syndrome have been credited to cortisone [144] Corticotrophin has been used to permit discontinuation of norepinephrine after shock has been controlled by the latter [310]

Antibiotics are of primary importance in the treatment of shock due to or complicated by infection In addition there is some experimental evidence suggesting that antibiotics may have a protective action in shock independent of their antibacterial effect [■]

Hypothermia [117] induced by body cooling to 30 to 32° C with the aid of antihistaminics such as Phenergan and with chlorpromazine (Thorazine) has been employed in the treatment of traumatic shock During hypothermia maintained for two or three days, wounded men have been transported to distant hospitals subjected to necessary surgery and subsequently rewarmed slowly to normal body temperatue

SYNCOPE

Syncope is characterized by a sudden and usually unexpected loss of consciousness and of locomotion If the subject is upright he falls Fainting swooning and neurocirculatory failure are used synonymously with syncope Certain instances of primary or neurogenic shock are associated with syncope

Syncope is usually a form of hyperacute circulatory failure due to extreme ischemia or anoxia of the brain It may also be caused by severe traumatic, metabolic or psychologic disturbances As a rule syncope results from an extreme fall in blood pressure or pronounced slowing or standstill of the heart The erect position extreme exertion and environmental heat are usually predisposing or precipitating factors

1 Vasodepressor Syncope

(a) Psychic or Neurogenic Fainting This is the simple faint of psychic or reflex (neurogenic) origin, the so-called vasovagal syncope [11] Fright pain or other powerful emotions, the sight of blood operations, etc , the experience of physiologic tests or instrumentation are among the causes of this type of fainting Syncope in these cases is the result of a sharp decline in blood pressure, possibly mediated by way of the carotid sinus It always occurs when the patient is in the erect position There are premonitory symptoms such as weakness nausea, sweating, pallor Slowing of the pulse and heart block may develop but these are not responsible for the syncope

This type of vasodepressor syncope is observed in the acute circulatory collapse which sometimes follows moderate venesections (300 to 900 cc blood), e g occasionally in healthy blood donors [205] The cardiac output may be only slightly diminished or unchanged as *reflex peripheral vasodilatation* [99] results in an increased speed of circulation whereby a relatively normal venous return is maintained Syncope is due to an *extreme fall in blood pressure associated with a corresponding diminution in peripheral resistance* This is to be contrasted with the sharp fall in cardiac output and the clinical picture of shock which follows the loss of larger amounts of blood (1500 to 2000 cc or more) [17] While the actual faint, i e , the loss of consciousness is due to cerebral ischemia caused by the fall in blood pressure, the associated symptoms such as pallor, nausea, and sweating are due to generalized stimulation of the autonomic nervous system possibly by some efferent arc from the brain (hypothalamus?)

Under the heading vasodepressor syncope are also included cases of primary shock (p 307) fainting with onset of acute infections, with strenuous exercise, during pregnancy, or pleural punctures and after vasodilating drugs such as nitrites and nitroglycerin Rarely a pregnant woman may faint when she lies flat on her back This has been attributed to stimulation of sensory receptors in the abdomen by the enlarged uterus and to pooling of blood in the lower extremities by pressure of the uterus on the inferior vena cava [190]

(b) Carotid Sinus Syndrome Infrequently, spontaneous attacks of unconsciousness result from hypersensitivity of the carotid sinus [208 59] These attacks can be reproduced by pressure over the carotid sinus In normal persons such pressure causes only a slight reduction in pulse rate (less than 6 beats per minute) and only a

slight reduction in blood pressure (less than 10 *mm Hg*) *The carotid sinus tends to become* sensitive in individuals past middle age and especially in those with hypertension or *atherosclerosis It is also possible that the end* organs (effector organs) such as the heart and blood vessels rather than the carotid sinus become *hypersensitive In subjects with a* hypersensitive carotid sinus the slightest pressure, such as that due to the passage of a *razor over the neck bending or turning of the* head in certain positions a high or tight collar may induce dizziness or syncope [33] Similar attacks *rarely result from the pressure* of an enlarged cervical gland or tumor [134] Tests of carotid sinus sensitivity should be *performed* with caution [4] In patients with a *thrombosis of one internal carotid artery* syncope may follow compression of the other *internal carotid artery* below the sinus but not after compression of the affected side [133] Syncopal attacks often associated with convulsions and attributed to a hypersensitive carotid sinus may occur in so-called pulseless disease [6, 103, 1, 4, 83] in which thrombosis of the carotid and subclavian arteries is secondary to panarteritis of unknown etiology

Carotid sinus hypersensitivity may result in (a) vasodepression with a sharp fall in blood pressure (b) cardiac slowing cardiac standstill or heart block with or without ventricular stand till or (c) reflex cerebral ischemia with convulsions and *focal neuro*logic signs Each reaction type may cause syncope The last or cerebral type of carotid sinus syncope *is unaccompanied by* changes in pulse or blood pressure and is associated with slow waves in the electroencephalogram

Rarely a *lesion on an afferent vagal arc* induces syncope by a vagovagal reflex by way of the carotid sinus In the case reported by Weiss and Ferris [59] *a patient with an esopha*geal traction diverticulum experienced attacks of fainting and cardiac standstill when swallowing The attacks could be reproduced by artificial distention of the esophagus and prevented by atropine Similar attacks may occur in patients with disease of the biliary tract [59] Glossopharyngeal neuralgia occurring with swallowing or talking was associated in one case with bradycardia cardiac arrest and syncope due to a carotid sinus reflex *in which the glossopharyngeal nerve was the* afferent arc [165] Intracranial section of the glossopharyngeal nerve on the affected side relieved the neuralgia and abolished the paroxysms of cardiac arrest and syncope

2 Postural Syncope and Chronic Orthostatic *Hypotension*

Postural syncope or orthostatic hypotension may be classified as (1) transient and (2) chronic orthostatic hypotension a definite clinical syndrome

Prolonged standing in a fixed position may result in syncope *even in the normal person* Arising from bed after a prolonged illness often causes faintness or syncope Cardiac asystole *and syncope may occur following an* episode of strenuous physical exertion [6, 44] In these instances syncope is probably due to pooling of blood in the vessels of the lower *extremities which is ordinarily prevented by* strong muscle tone by the pumping action of the *muscles* which aid the venous return to the heart and by normal vasoconstrictor adjustments which occur when the body assumes the erect position

Chronic orthostatic hypotension [51] or postural hypotension [illegible] is a chronic clinical syndrome characterized by an extreme fall in blood pressure dizziness and syncope as soon as the patient attempts motionless standing The pulse is usually unchanged during syncope but orthostatic tachycardia atrial fibrillation and ST segment depression in the electrocardiogram have been described

Chronic orthostatic hypotension is often due to serious underlying disease of the central nervous system [47] It may be *secondary* or *idiopathic* Secondary chronic orthostatic hypotension is observed most commonly in diabetic patients with neuropathy but also in patients with tabes dorsalis syringomyelia *Addison s disease and Simmonds disease* [186]

Idiopathic Chronic Orthostatic Hypotension There is also a definite syndrome of idiopathic *chronic orthostatic hypotension* which is characterized by the triad of anhidrosis impotence and orthostatic hypotension causing syncope [41, 175] This *occurs very predomi*nantly in males usually between the ages of 40 and 70 When the patient stands there is an abrupt progressive fall in blood pressure associated with weakness vertigo blurred vision and syncope The nausea and pallor which usually precede the vasodepressor faint are absent There is little acceleration of the pulse rate and the cardiac output *may fall* abnormally Lack of perspiration may be

partial or virtually complete is usually bilateral but may be unilateral Pilocarpine may induce sweating when heat does not Nocturia and incontinence may be associated with the impotence Orthostatic tachycardia may be associated[178] Symptomatic discomfort is usually most severe when the patient arises in the morning or after meals and exercise and in warm weather Pupillary abnormalities such as Horner s syndrome or other abnormal pupillary reactions may be present These various findings indicate that this form of chronic orthostatic hypotension is due to a disturbance in sympathetic innervation[181] (asympathicotonic hypotension[15]) The underlying pathologic lesion has been thought to lie in the hypothalamus where the sweating center and a subcortical vasomotor center are situated but may be due to high thoracic lesions of the spinal cord[104] Vercl[20] presented evidence which suggested that the disorder is due to a central failure of the carotid sinus reflex It has been demonstrated that patients with chronic orthostatic hypotension do not pool more blood in the lower portion of the body than do normal subjects[47, 191] But there is a deficiency in the reflex arteriolar and venous constriction which should compensate for the normal tendency to pooling of blood with assumption of the upright position[1] This results in a fall in blood pressure which is intensified by a reduction in the cardiac output[99, 155] due to a diminished venous return[1, 5] Deficiency of the vasoconstrictor reflex has been related to a sharp diminution in the secretion of norepinephrine and epinephrine[123]

3 Cardiac Syncope

This type is characterized by sudden loss of consciousness with slight or no premonitory symptoms It is due to cerebral anemia caused by ventricular asystole or ventricular fibrillation The underlying causes are either (a) heart block or ventricular fibrillation with Adams Stokes syndrome (p 390), (b) disorders of the heart beat such as sinoatrial standstill or sinoatrial block (p 383) paroxysmal tachycardia or atrial fibrillation[26] (c) frequent premature beats (d) calcific aortic stenosis and (e) ball valve thrombus and pedunculated tumor of the left atrium Cardiac arrest occurs because of failure of the ventricular pacemaker in cases of heart block or because of ventricular asystole due to carotid sinus and vagal reflexes The syncope of the Adams Stokes syndrome may be due to either ventricular standstill or fibrillation (p 377) In paroxysmal tachycardias especially atrial fibrillation loss of consciousness occurs either at the onset or end of the attack owing to ventricular standstill because of failure of the pacemaker with change of rhythm[26] When frequent atrial premature beats are encountered between syncopal attacks the attacks themselves are often associated with paroxysmal atrial tachycardia or fibrillation The syncope of aortic stenosis is usually due to relative cerebral ischemia on exertion but may be caused by reflex cardiac standstill through the carotid sinus or by heart block with ventricular arrest Mechanical obstruction of the mitral orifice especially when there is concomitant mitral stenosis, accounts for syncope in cases of ball valve thrombus or pedunculated tumor of the left atrium Obstruction and syncope are precipitated by change of bodily position

4 Anoxic Syncope

This includes cases of syncope occurring in high altitudes syncope with extreme exertion, or syncope on exertion in patients with underlying congenital heart disease aortic stenosis or decompensated chronic pulmonary disease In cases of *congenital heart disease* with a right to left shunt, such as the tetralogy of Fallot syncope may occur with exertion because of increased arterial oxygen unsaturation and consequent cerebral anoxia The increased muscular activity of exercise causes the venous blood leaving the muscles to become excessively unsaturated with oxygen This blood is shunted into the systemic circulation and further reduces the arterial oxygen saturation In *aortic stenosis* there may be maximal cardiac output and cerebral blood flow at rest With exercise the required increase in cardiac output cannot be effected at the same time that more blood may be shunted to the active muscles thus there is less for the cerebral circulation The effort syncope occurring during exercise in *cor pulmonale* may similarly be due to cerebral anoxia and ischemia caused by inability to increase the cardiac output combined with underlying hypoxemia The possible role of hyperventilation and hypocapnia or of hypercapnia is uncertain When syncope occurs in cor pulmonale as a result of depression of

respiration by morphine or the inhalation of oxygen the syncope is due to hypercapnia (carbon dioxide retention)

5 Tussive Syncope[131 132 133 11]

Loss of consciousness may occur promptly after a paroxysm of cough especially in patients with obstructive emphysema or other obstructive lesions of the trachea such as aneurysm or tumor It may also occur in children and in subjects with hysteria who bear down with glottis closed The loss of consciousness occurs usually during a period of acute hypotension following cessation of cough[132] When obstructive lesions of the trachea or bronchi or voluntary obstruction prevents rapid emptying of the thorax a paroxysm of coughing builds up such a high intrathoracic pressure that the venous return to the heart is obstructed with resultant fall in left ventricular output cerebral ischemia and syncope The intrathoracic pressure may exceed 300 mm Hg well above the arterial blood pressure Recent studies suggest that there is a concomitant marked rise in spinal fluid pressure and consequently in intracranial pressure and that the syncope is actually due to direct impairment of cerebral blood flow rather than to obstruction of the cardiac output by intrathoracic hypertension[132]

6 Hyperventilation Causing Syncope

Hyperventilation often occurring involuntarily may be associated with syncope Such syncope is seen most frequently in adolescent girls and young women of neurotic temperament but I have observed it also in older women and in men The syncope usually develops gradually often preceded by dizziness and the loss of consciousness may be incomplete and is generally very brief A careful history may reveal other manifestations of the hyperventilation syndrome such as numbness and tingling of the hands feet and face visual disturbance or tetany The syncope is probably due to the diminished blood flow caused by low blood carbon dioxide tension (hypocapnia) but an associated fall in blood pressure may be important

7 Other Types of Syncope

Under this heading may be included cases of syncope due to severe head injuries to severe local vascular disease of the brain to drug sensitivity (e g after procaine injection) to hypoglycemia caused by insulin shock or an Addisonian crisis Postural hypotension induced by atropine has been reported[109 136]

8 Hysterical Fainting

Hysterical fainting is a special type of loss of consciousness of profound psychologic origin It occurs without alteration of pulse or blood pressure and without electroencephalographic abnormalities[171] It may be due to hyperventilation to neurogenic vasodepressor reflex or to closure of the glottis as in tussive syncope

9 Aviation and Syncope

Syncope presents an important problem in flying especially for pilots In a study of 500 cases of syncope involving pilots and air crew 42 per cent were interpreted as primarily of emotional origin 24 per cent as primarily neurogenic 31 per cent as primarily cardiovascular and 3 per cent unclassified[172] Hyperventilation of emotional origin was a frequent factor in the production of convulsions

Directly associated with aviation are the cases of syncope due to cerebral anoxia induced by low atmospheric pressure[172] when flying at great heights or by positive acceleration in the long axis of the body (blackout) or when the plane decelerates during ascent from a sharp dive at maximum acceleration During rapid ascent of a plane decompression with release of nitrogen and other gaseous bubbles from solution in the blood may cause aeroembolism with cerebral vascular occlusion and possible syncope or death

Differential diagnosis of the various types of syncope can usually be made by a very detailed history of the events and symptoms preceding during and after the attack by a careful examination and sometimes by special tests (carotid sinus pressure electrocardiography electroencephalography etc) and by observing the effects of drugs An excellent discussion has been presented by Engel[81]

TREATMENT OF SYNCOPE

A recumbent or head down position abolishes most attacks of syncope Preferably the patient should be placed in the Trendelenburg position or he should be in a supine or prone position with his legs elevated[133]

In the cases of frequent syncopal attacks (postural hypotension) the cause should be treated if possible (large varicose veins Addison s disease) Leg bandages and abdominal binders may be employed to help the venous

return Training the patient with a head up bed 20 degrees above horizontal has been recommended in the treatment of chronic postural hypotension [5] The most effective treatment is the continued administration of the sympathomimetic (vasoconstricting) drugs

Isopropylnorepinephrine (Isuprel) 10 to 15 mg may be taken sublingually to abort an attack if there is adequate warning Ephedrine sulfate 25 mg or amphetamine 5 to 10 mg [37] may be given orally one to four times daily especially in the earlier part of the day Paredrine hydrobromide has a more sustained action and less central effects and may be given orally in 60 mg doses three times daily Sometimes it is more effective to give a single daily dose of 100 to 160 mg of Paredrine one-half hour to an hour before arising Similar advantages apply to Neo-synephrine which has been found effective in 20 mg doses three times daily (following larger initial doses) after ephedrine and amphetamine had failed to control the syncopal attacks Paredrine and Neo synephrine may be used parenterally to control the syncope of spinal anesthesia (p 307) It may be necessary to combine the sympathomimetic drugs with mild sedatives to counteract nervous excitation or sleeplessness

The sympathomimetic drugs are also used in cases of syncope due to a hypersensitive carotid sinus syndrome In addition tincture of belladonna 10 to 15 minims three times daily or atropine sulfate 0 3 mg ($\frac{1}{200}$ grain) three times daily may be helpful In some instances surgical denervation of the carotid sinus (after a preliminary therapeutic test with procaine infiltration) may be advisable to eliminate the attacks [3] Greeley et al [85] reported relief of the carotid sinus syndrome within hours or a few days after irradiation of one or both carotid sinuses Two or three treatments were given on alternate days a dose of 200 roentgens (measured in air) was administered to a 5 cm square portal and the total dosage averaged 500 roentgens if one side was treated and 800 roentgens if both The factors were 200 to 220 kV with a 2 mm filter of copper and a 1 mm filter of aluminum and a 50 cm target skin distance

The use of molar sodium lactate epinephrine Isuprel [178] and other sympathomimetic drugs in syncope of Adams Stokes syndrome is discussed elsewhere (p 393) The use of an electrical cardiac pacemaker[219] may be undertaken when there are very frequent episodes of ventricular asystole despite sympathomimetic drugs Syncope due to procaine sensitivity should be treated with barbiturates and not with sympathomimetic agents

CARDIAC ARREST (See pp 1108 and 394)

SUDDEN DEATH

Sudden death denotes the *quick* and *unexpected* termination of life This may include death instantaneously or within a few minutes sudden syncope with deepening and fatal coma or an acute illness without unconsciousness which is unexpectedly fatal within twenty four hours [146]

PATHOLOGIC PHYSIOLOGY

Sudden death results from sudden irreversible and intense cerebral anoxia The responsible mechanisms are similar to those causing syncope or shock but more rapid and severe and hence irreversible (But see p 583)

These mechanisms include (a) sudden local traumatic toxic vascular or metabolic injury to the brain (b) exsanguinating hemorrhage with medullary anoxia or pericardial hemorrhage causing cardiac tamponade (c) massive pulmonary embolism with obstruction of blood flow and cerebral anoxia (d) ventricular asystole

The last group is of special interest to the cardiologist Often in instances of sudden death postmortem examinations fail to reveal the cause Coronary atherosclerosis or other cardiac disease is frequent but insufficient in degree to explain the sudden end [123] It is believed that death in such cases is due to a physiologic disturbance resulting in cessation of the heart beat Cessation of the heart beat may be due to cardiac standstill or to ventricular fibrillation [194]

Belief in the causal relationship of ventricular fibrillation to sudden death is based on (a) observations of this arrhythmia prior to death of experimental animals especially following coronary artery ligation,[91] and (b) its presence in electrocardiographic tracings taken by chance in patients who died during the recording [82] On the other hand Weiss [97] stressed the possible relation of cardiac standstill (caused by carotid sinus and vagal reflexes or heart block) to sudden death Cardiac standstill is sometimes observed in

exposed hearts when sudden death occurs during operation In a recent study of terminal electrocardiograms Stroud and Feil[184] found that sudden death was associated as often with cardiac standstill as with ventricular fibrillation In the presence of coronary or cardiac disease the myocardium is especially susceptible to both of these forms of sudden death

ETIOLOGY AND PATHOLOGY

Cases of sudden death are usually seen by the coroner A physician summoned to see an individual who died suddenly must be cautious in excluding factors of violence and poisoning even when there is no overt evidence and even when the *individual was known to have some competent producing* cause No death certificate should be issued without the approval of the coroner or official medical examiner if the physician was not in attendance at the time of death or if there is a claim of trauma as the cause of death

Excluding deaths due to trauma or poisoning the commonest causes of sudden death[14, 168] are (1) diseases of the heart and aorta (2) respiratory diseases especially pneumonia (3) cerebral complications especially those associated with hemorrhage (4) diseases of the digestive and urinary tracts

Among the precipitating causes are severe exertion[107] especially in warm weather *straining at stool anesthesia aspiration of* body cavities fright and other powerful emotions

Heart disease is by far the commonest cause of sudden death and coronary atherosclerosis accounts for at least 60 to 80 per cent of these sudden cardiac deaths[57, 149] Attention has recently been drawn to the frequency of sudden death in young men with advanced coronary atherosclerosis but without coronary occlusion or myocardial infarction[75, 14, 217] But sudden death may result at the onset of an acute coronary occlusion or from ventricular rupture following myocardial infarction Massive pulmonary embolism is a common cause of death in patients with acute myocardial infarction as well as in patients bedridden for other reasons

Calcific aortic stenosis is the commonest valvular lesion associated with sudden death but the latter may occur with any other valvular or myocardial disease

Sudden death occurs more often with syphilitic than with rheumatic aortic insufficiency probably because of the accompanying ostial stenosis in the former Sudden death in syphilitic aortitis[119] may also be due to rupture of an aortic aneurysm

Among natural causes of sudden death to be remembered are acute respiratory infections and congenital heart disease in infants coronary atherosclerosis rupture of a congenital cerebral aneurysm tubal rupture in ectopic pregnancy brain tumor and fulminating meningitis in young adults, coronary artery disease and syphilitic aortitis dissecting aneurysm of the aorta and acute gastrointestinal bleeding in middle age and beyond

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PART III

THE CARDIAC ARRHYTHMIAS

Chapter 13

DISTURBANCES IN IMPULSE FORMATION

CLASSIFICATION OF DISORDERS OF THE HEART BEAT

In general cardiac arrhythmias result from disturbances in impulse formation or impulse conduction and these may be further subdivided as follows

- I Disturbances in impulse formation
  - A Sinoatrial (sinus) rhythms (nomotopic rhythm)
    - 1 With abnormal rate
      - a Sinus tachycardia
      - b Sinus bradycardia
    - 2 With irregular sequence of impulse formation
      - a Sinus arrhythmia
      - b Sinus arrest and atrial standstill
      - c Ventricular and cardiac standstill
  - B Ectopic rhythms (heterotopic rhythms)
    - 1 Escape rhythms (nodal rhythm and idioventricular rhythm)
    - 2 Premature contractions (extrasystoles)
    - 3 Paroxysmal tachycardia
    - 4 Atrial flutter
    - 5 Atrial fibrillation
    - 6 Ventricular tachycardia
    - 7 Ventricular fibrillation
- II Disturbances in conduction of the cardiac impulse
  - A Sinoatrial heart block
  - B Atrioventricular heart block (partial and complete)
  - C Bundle branch block
  - D Short P R interval with prolonged QRS

The above classification is based on the physiologic disturbances in the initiation and propagation of the cardiac impulse It is useful in the understanding of the associated electrocardiographic abnormalities From the practical viewpoint of bedside diagnosis it is simpler to observe whether the cardiac rhythm is regular or irregular and whether the rate is unusually rapid (tachycardia) unusually slow (bradycardia) or normal

Tachycardias which are regular include (1) sinoatrial (sinus) tachycardia (2) paroxysmal atrial tachycardia (3) ventricular tachycardia and (4) atrial flutter with 1 1 response or with unchanging degree of block Irregular tachycardias include (1) atrial fibrillation (2) atrial flutter with varying block and (3) sinus tachycardia with numerous premature beats

Bradycardias with regular rhythm include (1) sinus bradycardia (2) nodal rhythm (3) severe partial heart block with constant degree of block and (4) complete heart block Irregular bradycardias include (1) sinoatrial bradycardia with marked sinus arrhythmia or frequent premature beats and (2) partial heart block with frequent dropped beats or changing degree of block

Irregular rhythms with normal heart rate include frequent premature beats atrial fibrillation with ventricular rate slowed by digitalis sinus arrhythmia and partial heart block with dropped beats

SINUS TACHYCARDIA

The normal heart rate of adults at rest varies between 60 and 90 per minute while that of infants ranges between 100 and 150 Sinus tachycardia denotes that the cardiac impulse arises normally in the sinoatrial node but that the rate is increased above 100 per minute (adults) Knowledge of the individual s normal heart rate under given conditions is a better basis for determining the existence of tachycardia than arbitrary levels Ordinarily the heart rate in sinus tachycardia does not exceed 160 per minute a feature distinguishing it from that of paroxysmal atrial or ventricular tachycardia

The *electrocardiogram* is characterized by abbreviation of the P P intervals below 0 6

second and by recurrence of the P waves at regular intervals each followed by a QRS complex Occasionally, when the rate exceeds 150 per minute, the P waves may become fused with the preceding T wave The reduction in the cardiac cycle is chiefly at the expense of the diastolic period

Vagal depression and accelerator stimulation in varied degree account for sinus tachycardia

Physiologic sinus tachycardia results from emotion exercise digestion, and other causes Voluntary acceleration of the heart rate has been observed[27] Certain drugs such as atropine and amyl nitrite may be used clinically to produce sinus tachycardia Among pathologic conditions associated with sinus tachycardia are fever, hyperthyroidism, anemia acute hemorrhage shock congestive heart failure and cardiac neurosis Tachycardia on assumption of the upright position occurs in some cases of chronic postural hypotension (p 313) and occasionally in cases of pheochromocytoma (p 1025)

Examination of the heart and pulse discloses a regular rhythm with a rate exceeding 100 per minute Differentiation from other tachycardias with *regular* rhythm may be made from the electrocardiogram or surmised on clinical grounds (p 378) There may be no subjective symptoms, or there may be disagreeable palpitation fatigue and breathlessness as in other tachycardias (p 346)

The clinical significance depends on the basic cause The tachycardia subsides when the underlying cause is removed Sometimes tachycardia is noted without apparent cause An unsuspected hyperthyroidism or anemia may be responsible and the possibility of their presence should be investigated Occasionally a persistent sinus tachycardia disappears only after the elimination of tobacco alcohol excessive coffee or sympathomimetic drugs such as ephedrine, dextroamphetamine or the like

SINUS BRADYCARDIA

Sinus bradycardia denotes that the cardiac impulse arises normally in the sinoatrial node but that the cardiac rate is less than 50 per minute

The *electrocardiogram* is characterized by prolongation of the P-P interval to 1 second or more, but the P waves recur regularly and are each followed by QRS complexes Occasionally in bradycardias of vagal origin sinus arrhythmia (see below) is associated, and the P P intervals are somewhat irregular The P R interval tends to be prolonged in sinus bradycardia Slowing of the heart rate involves predominantly an elongation of diastole (T-P interval)

The *mechanism* is probably an increase of vagal tone or a diminution of sympathetic tone or both

Normally, heart rates of 50 per minute or less are sometimes observed during sleep and are not uncommon during pregnancy Sinus bradycardia is fairly common among those engaged in strenuous labor and among trained athletes Rates as low as 36 to 40 per minute have been observed in distance runners with normal hearts Under pathologic circumstances sinus bradycardia may be associated with cerebral lesions with increased intracranial pressure, coronary heart disease (occasionally) convalescence from infectious disease myxedema icterus and in patients treated with ACTH or cortisone

There are usually no clinical symptoms of sinus bradycardia but dyspnea palpitation, precordial pain dizziness, faintness or syncope may be associated with extremely slow cardiac rates[40] Syncopal attacks may be due to excessive bradycardia or cardiac asystole[40]

Examination of the heart and pulse discloses a regular rhythm with slowing of the heart rate below 50 per minute But the rate may be increased by exercise emotion atropine or any other factor which diminishes vagal or increases sympathetic tone

Sinus bradycardia must be differentiated from a slow nodal rhythm and from heart block The presence of the normal systolic collapse in the jugular vein and the absence of jugular pulsations during the long diastolic pause may be distinctive of sinus bradycardia in contrast to nodal rhythm or heart block In heart block, atrial pulsations may be visible in the cervical veins and atrial cardiac sounds may be audible during the pauses between heart beats The electrocardiogram is usually necessary for a definite diagnosis Sinus bradycardia may be indistinguishable from prolonged sinoatrial block with 2 1 rhythm (p 383)

Usually no treatment is necessary If syncope occurs treatment is that described under Adams-Stokes syndrome (p 390)

SINUS ARRHYTHMIA (PHASIC ARRHYTHMIA, JUVENILE ARRHYTHMIA)

The cardiac impulses arise normally in the sinoatrial node but their rhythmicity varies. This gives rise to alternating periods of slower and more rapid cardiac rates. The longest and shortest R-R intervals differ by 0.12 second or more. The variations are usually, but not always, related to respiration, the heart rate increasing with inspiration and diminishing with expiration (respiratory arrhythmia).

The *electrocardiogram* discloses P waves each followed by QRS complexes in normal succession, but the P-P intervals form alternate series of shorter and longer cycles. The changes in length are virtually confined to the T-P interval (Fig. 62). The configuration of the P wave may show slight alterations suggesting shifting sites of origin of the cardiac impulse, but all within the sinoatrial node. The P-R interval may be relatively longer after a short R-R interval, i.e., during the more rapid rates, than during the slower cycles. This has been related to the Wenckebach phenomenon[28] (p. 386) or to a lower origin of the impulse in the sinus node and therefore a lesser distance to the ventricular conduction system. On the other hand, strong vagal tone may also tend to prolong the P-R interval.

Mechanism. Careful analysis of electrocardiograms with normal sinus rhythm and rates under 80 per minute disclose that there is no absolute regularity and that cycle lengths vary slightly but definitely. This is probably due to physiologic phasic variations in the vagal (and sympathetic?) tonus. Sinus arrhythmia is merely an exaggeration of this normal tendency. A chronotropic inhibitory effect of the vagus nerve may cause a *shift of the pacemaker* from the cephalic position to the middle or tail of the sinoatrial node, as suggested by changes in the form of the P wave and as indicated by intracardiac electrocardiography.[43] Impulses from the respiratory center and lungs at the height of inspiration depress the vagus center and accelerate the cardiac rate. Sinus arrhythmia is commonest in hearts with bradycardia, presumably because there the vagal influence tends to be maximal. Sinus arrhythmia may be associated with other influences which affect vagal tonus independently of the respiratory phase.

Sinus arrhythmia occurs commonly among children and among the aged.[28] It is often observed during rheumatic fever, convalescence from infectious diseases, following digitalization, and in diseases of the brain with increased intracranial tension, all conditions associated with vagal stimulation or increased vagal tonus.

Clinically, sinus arrhythmia is recognizable by the fairly regular alternation of several rapid heart or pulse beats with a similar cycle of slower beats. The relation of the rapid beats to inspiration and the slow beats to expiration is diagnostic. Intensification of the arrhythmia by deep breathing or its abolition by breath holding, exercise or atropine may also be helpful in diagnosis. Rarely an electrocardiogram is required to distinguish with certainty sinus arrhythmia from atrial fibrillation with slow ventricular rate or from partial atrioventricular block with varying P-R interval.

As a rule sinus arrhythmia is of no clinical importance and requires no treatment. When accompanied by intense bradycardia, it may be associated with attacks of dizziness. When sinus arrhythmia results from vagal stimulation secondary to serious cerebral disease or the like, the outlook is that of the underlying disease.



Fig. 62. Sinus arrhythmia. A woman, aged 28, with diabetic acidosis but without heart disease. Lead III. Progressive decrease, then increase in length of cardiac cycles. Effect chiefly on length of T-P interval.

SINUS ARREST AND ATRIAL STANDSTILL

For general discussion of Cardiac Arrest see pages 391 and 1108.

Sinus arrest (sinoatrial standstill or sinus pause) denotes a pause in the cardiac rhythm due to a momentary failure of the sinus node to initiate an impulse.

The *electrocardiogram* is characterized by a

prolonged diastolic pause between two PQRST complexes which are entirely normal (Fig 63) The pause is not an exact multiple of the normal P P cycle

The *mechanism* is probably a reflex vagal stimulation through the carotid sinus or a direct stimulation of the vagal center

Sinus arrest may occur after gagging or stimulation of the pharynx It may be observed in patients with a hypersensitive carotid sinus Sinus arrest and sinus arrhythmia are sometimes associated both resulting from conditions which stimulate the vagus nerve

Sinus arrest is usually of no clinical significance but if the pause is sufficiently long dizziness faintness or even syncope may ensue

Clinically sinus arrest is recognized by the omission of a beat (dropped beat) at the cardiac apex as well as at the wrist Sinus arrest may be indistinguishable from sinoatrial block (p 383) It must be differentiated from the pause of dropped beats in partial heart block (p 385) and the compensatory pause following an early premature beat

Atrial standstill denotes a pause in atrial contraction, while the ventricle contracts in response to stimulation by its own pacemaker [47] Atrial standstill is secondary to either sinus arrest or sinoatrial block Magnasson[61] reported 3 cases of his own and 31 cases collected from the literature

The *electrocardiogram* shows a regular sequence of ventricular complexes, but one or more P waves are absent Bradycardia is commonly associated

Mechanism When the sinoatrial node fails to initiate an impulse or the impulse is blocked from reaching the atrium, there is no atrial contraction However a pacemaker of lower rhythmicity (infra) in the a v node bundle or ventricle, activates the ventricle and causes contraction

The *cause* of atrial standstill is usually digitalis or quinidine intoxication but organic heart disease is often present

Clinically, the rhythm is regular, but there may be intense slowing of the heart An electrocardiogram is essential for diagnosis When atrial standstill is due to digitalis or quinidine, these drugs should be stopped and if necessary, resumed later in smaller dosage

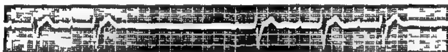


Fig 63 Sinus arrest or sinus inertia A man aged 73 with coronary artery disease Lead II Pauses without atrial or ventricular contraction Sinoatrial block not excluded but less probable because pauses are not multiples of normal P P interval There are associated conduction disturbances

ECTOPIC BEATS AND ECTOPIC RHYTHMS

All parts of the conduction system possess the property of excitability and rhythmicity, that is of initiating impulses and exciting contraction But the degree of rhythmicity, i e the rapidity with which impulses are formed and released, varies Normally the sinoatrial node has the greatest rhythmicity and dominates the rhythm of the heart It is therefore termed the pacemaker Lesser degrees of rhythmicity are possessed by the atrioventricular node, the a v bundle and the ventricular specialized tissue, in that order Thus while the s a node emits impulses at 70 to 80 per minute, the a v node initiates them at 40 to 60 per minute and the bundle and lower centers at less than 40 per minute The impulses released by these other centers are nullified by the more frequent sinus impulses However when the rhythmicity of the sinoatrial node is depressed or the rhythmicity of some other center of the heart is enhanced above that of the sinus node the lower center may control the heart rhythm and become the pacemaker Whenever isolated cardiac beats are excited by some center other than the sinus node, they are termed ectopic beats When a more continuous rhythm is initiated by a focus outside the sinus node it is termed an ectopic rhythm

ESCAPE RHYTHMS

Escape rhythms are those initiated by lower centers when the sinoatrial node fails to initiate impulses when its rhythmicity is depressed, or when its impulses are completely blocked When the a v node becomes the pacemaker for a single beat it is termed a nodal escaped beat, when it becomes pacemaker for a continuous period, nodal rhythm

appears. If the atrioventricular node activates the ventricles, whereas the atria are activated by the sinoatrial node, the rhythm is termed atrioventricular dissociation, not nodal rhythm. If the s a node and a v node are sufficiently depressed or fail to initiate impulses, a focus in the bundle or ventricles controls ventricular contraction either for isolated beats (ventricular escape) or for a continuous rhythm termed idioventricular rhythm.

Atrioventricular (Nodal) Rhythm. Wandering Pacemaker

Experimentally, nodal rhythm can be produced by cooling, clamping, or chemical destruction of the sinoatrial node[5, 16] and occasionally by vagal stimulation. The rhythm of a lower center thus released represents an escape rhythm, and the cardiac rate is slow, averaging 40 to 60 per minute.[9] But nodal rhythm may be associated with a normal rate and a v nodal tachycardia has also been described (pp. 344–345).

Occasionally, isolated beats are controlled by the a v node while others are controlled in their normal fashion by the sinoatrial node. This phenomenon is termed wandering or shifting pacemaker. Such shifts in pacemaker occur whenever the rates of impulse formation in the sinoatrial and atrioventricular nodes are almost identical. Then slight physiologic changes in vagal tonus may modify these rates of impulse formation sufficiently to permit one or the other of the nodal centers to gain control of the heart rate.[16, 31] Pressure on the carotid sinus or eyeball (oculovagal reflex) may induce transient a v beats or rhythm interspersed among stretches of sinus rhythm. Occasionally the slight variation in vagal tonus caused by sitting up from the recumbent position may result in transient nodal rhythm.[■] The intravenous administration of Neo-synephrine in humans, presumed to cause reflex vagal stimulation, suppresses the sinus node with consequent bradycardia or atrial standstill, or there may be wandering of the pacemaker or nodal rhythm.[17] Other beats or rhythms dominated by the a v node are nodal premature beats (p. 335) or nodal tachycardia (pp. 344–345). These represent enhancement of nodal rhythmicity rather than primary depression of the sinus node, but both may coexist.

The Electrocardiogram. With *isolated nodal escape beats* there is a sinus pause followed by a normal QRS complex, while the P wave is usually inverted and precedes, fuses with, or follows the QRS complex (Fig. 64). The P wave is usually altered in configuration because the origin of the atrial activation wave in the a v node and its course differ from the normal. As a rule the s a node resumes its role as pacemaker after isolated nodal or other ectopic atrial escape beats. But several beats with varying position and configuration of the P wave occur before sinus rhythm is reestablished. The path of the pacemaking stimuli may be followed by esophageal leads and atrial vectorcardiograms.[17]

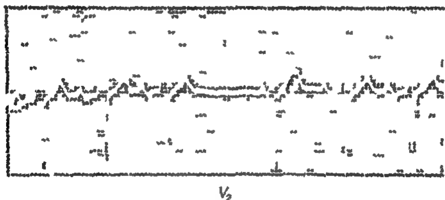


Fig. 64. Sinus arrest after third beat. This is followed by an escaped nodal beat.

With continued a v nodal control (*nodal rhythm*) the QRS complexes are normal and follow in regular sequence at a rate of 40 to 50 per minute. This denotes that the cardiac impulse follows its normal course in depolarizing the ventricles. On the other hand, the a v nodal impulse must be conducted retrograde toward the s a node and atria in acti

vating these chambers Such caudiocranial conduction in nodal rhythm may be demonstrated by esophageal leads[86] This modifies both the position and configuration of the P waves It is assumed that when the cardiac impulse arises in the head or coronary sinus portion of the a v node (coronary sinus rhythm)[78] atrial depolarization precedes that of the ventricles and the P wave precedes the QRS, when it arises in the body or midportion, both atria and ventricles are simultaneously activated and the P wave is lost in the QRS, when the impulse arises in the tail of the a v node it reaches the ventricles prior to the atria and the QRS precedes the P wave But even when the P wave in nodal rhythm precedes the QRS as it does normally the P-R interval is shortened (0 11 second or less) because the distance traversed by the impulse from the a v node to the ventricles is always shorter than from the sinus node In coronary sinus rhythm i e when the impulse



Fig 65 Nodal rhythm A man aged 56 with healed anterior wall infarction Lead II Inverted P waves following ventricular deflection

arises in the uppermost portion of the atrioventricular node the P R interval is within the range of normal The retrograde direction of the a v nodal impulse as it activates the atria causes an inversion of the P wave in leads II and III (Fig 65) The effect on lead I depends on whether the depolarizing process runs from right to left as normally or is altered accordingly P_1 may be upright diphasic or inverted

Rarely a v nodal rhythm is coupled with premature contractions of sinoatrial atrial or ventricular origin[..., 19] Nodal rhythm may be associated with atrioventricular block[47] Upper atrioventricular nodal beats have been precipitated by ventricular extrasystoles with retrograde conduction[78]

Clinically, nodal rhythm is observed in conditions which depress the rate of impulse formation in the sinoatrial node or which prevent the sinus impulses from reaching and activating the atria (sinoatrial block) Usually underlying heart disease is present but physiologic or pathologic influences which increase vagal tone are contributory or precipitating factors in the initiation of a-v rhythm Hypertension and coronary artery disease are commonly found in cases of coronary sinus rhythm[78] A v rhythm has been attributed to the impairment of the blood supply to the sinoatrial node especially in elderly persons with high vagal tonus In such persons deep breathing digitalis or anesthesia may induce a v (nodal) rhythm Nodal rhythm has been observed in association with acute coronary occlusion[53] in various infectious diseases[..] especially active rheumatic fever[..] and after atrial flutter But a v nodal rhythm also occurs in apparently normal hearts, both as a result of vagal stimulation by carotid sinus or ocular pressure[37] and paradoxically after the parenteral administration of atropine[..] A v nodal rhythm has also been observed after the administration of digitalis[66] quinidine[33] and Neo synephrine[17]

Despite this variety of circumstances under which it may develop, actually a v rhythm occurs relatively infrequently It is almost always a transient phenomenon alternating with sinus rhythm Usually a-v rhythm persists for brief runs but occasionally it may persist for several days or weeks

Clinical symptoms are uncommon and rarely distressing But there may be disturbing palpitation or a choking sensation or fullness in the neck due to simultaneous ventricular and atrial contraction The latter forces the atrial contents into the cervical veins as the tricuspid valve is shut For this reason also there may be an intensification of the first cardiac sound and there may be a prominent pulsation in the cervical veins due to the abnormal amplitude of the atrial (a') wave

Diagnosis usually requires electrocardiographic study (p 327) but a v rhythm may be suspected from the bradycardia and from the atrial systolic regurgitation waves in the cervical veins A jugular pulse tracing with simultaneous electrocardiogram may show "a waves occurring synchronously with the QRS complexes Bradycardia due to heart

block may be distinguished by the presence of atrial waves in the long diastolic intervals between beats. Esophageal electrocardiograms indicate not only the presence of nodal rhythm but the probable site of origin and course of the impulse.

Treatment either is unnecessary, is directed toward the underlying disease (e.g. coronary disease) or consists in removal of the causative agent (digitalis). Nodal rhythm can usually be abolished by atropine or exercise.

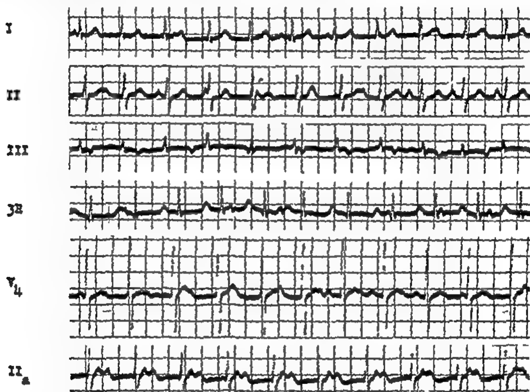


Fig 60 Complete atrioventricular dissociation in acute rheumatic fever. Atrial rate (lead V 3R) 100 per minute, ventricular rate 120 per minute. In lead II there is first degree heart block with P R 0.3 second.

Atrioventricular Rhythm with Reciprocal Beats. In most instances of a-v (nodal) rhythm the nodal impulse activates the ventricles and also is transmitted retrograde to activate the atria. Occasionally this same retrograde nodal impulse, after effecting an atrial contraction, may retrace its path to the a-v node and continue through the bundle and bundle branches to induce another ventricular contraction.[21] This additional contraction is termed a reciprocal beat, and when many such beats occur there is a reciprocal or reciprocating rhythm.[7]

Reciprocal beats occur as a rule in that type of a-v rhythm in which the ventricles contract before the atria and in which the atrial activation is so delayed that the ventricle is no longer refractory and can respond to the returning atrial (nodal) impulse. Often there is a progressive increasing delay in retrograde conduction until finally a reciprocal beat occurs, resembling a reversed Wenckebach period (p 386). This delay in retrograde conduction of the a-v nodal impulse is usually induced by carotid sinus pressure or digitalis therapy.

The *electrocardiogram* shows the QRS complex of a-v rhythm followed by an abnormal (nodal) P wave after an interval which is longer than usual. This P wave is then followed rapidly by another QRS complex. The result is a succession of QRS complexes (ventricular beats) resembling bigeminy or coupling (p 332) ordinarily seen when a premature ventricular beat (extrasystole) follows a normal ventricular contraction.[35] The term "return extrasystole" is sometimes applied to the reciprocal beat.

Atrioventricular Rhythm and Atrioventricular Dissociation. I have stated that in atrioven

tricular rhythm the nodal impulse is usually conducted retrograde as well as forward and activates the atria as well as the ventricles Sometimes possibly as a result of retrograde (unidirectional) atrial block the nodal impulse activates the ventricles but not the atria [77] In such cases the sinus node may continue to activate the atria while the a v node controls only the ventricles in spite of the more rapid stimulus formation in the a v as compared with the s a node This independence of atrial and ventricular contractions in response to different pacemakers is atrioventricular dissociation (Fig 66) The ventricular rate, controlled by the a v node, may exceed that of the atria which are responding to a depressed sinoatrial node This type of a v dissociation is usually the result of digitalis or of infections such as rheumatic fever Another form of a v dissociation may result from complete atrioventricular block in which neither sinus nor a v nodal impulses reach the ventricles and the latter respond to a pacemaker in the bundle below the block (see idioventricular rhythm) Complete a v block with dissociation is distinguished by more frequent atrial contractions than ventricular, while in the type under discussion the ventricular rate is more rapid than the atrial

A V Dissociation with Interference Beats (Interference Dissociation) In the cases of atrioventricular rhythm and dissociation, an occasional sinus impulse may succeed in activating the ventricles as well as the atria despite the higher rate of impulse formation in the a v node The ventricular contraction in response to a sinus impulse interrupts the usual contractions in response to a v nodal impulses and is termed an *interference beat* The combination of interference beats with atrioventricular dissociation is termed *interference dissociation*[57] (Fig 67)

Atrioventricular dissociation is most commonly due to digitalis toxicity and occasionally to quinidine It may be observed in association with rheumatic carditis or coronary heart disease

Ordinarily in a v rhythm with dissociation, the slow sinus impulses cannot activate the ventricles because the a v node and lower conduction system are refractory when the sinus impulse arrives Because of continuous although slight variations in the rate of formation of sinus impulses and similar variations in the time relationship of sinus and a-v nodal impulses, a sinus impulse occasionally arrives at the a v node when the latter is not refractory, traverses the bundle and its branches and activates the similarly nonrefractory ventricles The sinus ventricular beat follows the a v nodal ventricular beat after an abnormally brief interval and gives the appearance of a coupled extrasystole (p 332) Dressler and associates[20] described 2 cases of atrioventricular dissociation with interference in the presence of 2 1 atrioventricular block This arrhythmia, sometimes erroneously diagnosed as complete heart block differs from ordinary interference dissociation in that the ventricular rhythm is slower than sinus rhythm but faster than one half the sinus rhythm

The *electrocardiogram* in interference dissociation is characterized by QRS complexes of normal configuration (a v nodal origin) occurring independently of and at varying intervals from normal sinus P waves The P wave may be lost in one (nodal) QRS and then follow successive (nodal) QRS complexes at progressively longer intervals until it occurs so late that it is followed by a (sinus) QRS complex which occurs prematurely in response to the sinus impulse The irregularity simulates premature atrial systoles These interference beats are distinguished from reciprocal beats (p 329) by the normal upright sinus P waves between the coupled QRS complexes (Fig 67) In reciprocal beats the premature QRS follows a returning a v nodal impulse which is represented by a deformed or inverted P wave Both accompany a v nodal rhythm but reciprocal beats occur only if there is no complete retrograde atrial block to the a v nodal impulse while interference beats occur only in the presence of such a retrograde block which is responsible for the a v dissociation Both reciprocal and interference beats occur in a-v rhythm in which the ventricular rate is slightly more rapid than the atrial and which is usually the result of sinoatrial depression or sinoatrial block caused by digitalis or in acute infections such as rheumatic fever

Idioventricular Rhythm

We have seen that depression of the rate of impulse formation in the sinoatrial node or block of sinoatrial impulses may permit the a v node to become the pacemaker of the heart for isolated beats (nodal escape beats)

or for continuous periods (a v nodal rhythm) Similar depression of the a v as well as the sinoatrial node (carotid sinus or ocular pressure) or a block of a v conduction (digitalis organic lesions) may permit still lower automatic centers in the main a v bundle or in the specific tissue of one of the ventricles to assume control of the heart beat When single ventricular impulses pace the heart isolated ventricular escape beats are observed When the lower center maintains more continuous control there is idioventricular rhythm or ventricular automatism The atria remain under sinoatrial control

Idioventricular rhythm is observed most commonly in cases of atrioventricular block (p 386) in which impulses from the s a or a v node are prevented from reaching the ventricles The pacemaker probably arises in the a v bundle below the site of obstruction for the configuration of the QRS is normal (*supraventricular type*) denoting a normal pathway of the wave of ventricular excitation The ventricular rate is usually less than 40 per minute Since the atria are independently activated by the sinus node the P waves are of normal configuration and occur at rates of 70 to 80 per minute Thus as in some cases of a v rhythm idioventricular rhythm is accompanied by atrioventricular dissociation Since the ventricular complex in idioventricular rhythm is usually identical with that of a v rhythm the two conditions may be indistinguishable when there is a v dissociation The ventricular rate is usually more rapid (above 40) in a v rhythm there is usually a prolonged pause (preautomatic pause) before the onset of ventricular automatism, and carotid sinus pressure (vagal stimulation) usually slows the ventricular rate in a v but not in idioventricular rhythm since the vagus does not extend below the a v node Retrograde conduction to the atria rarely if ever occurs in idioventricular rhythm but is common in a v rhythm In the presence of such retrograde conduction a v rhythm is generally easily distinguishable by the presence of P waves usually inverted in leads II and III at abnormally short distances preceding or following the QRS complex

When the idioventricular pacemaker is situated below the bundle of His the QRS complex has a bizarre configuration characterized by widening slurring and notching while the T wave is often opposite in direction to the main QRS deflection This abnormal appearance denotes an abnormal origin and course of ventricular excitation (p 335) The electrocardiographic appearance of the ventricular *complex (QRST) is identical with that of an* extrasystole (premature beat) but may be distinguished by its occurrence after a prolonged pause instead of prematurely In both of these the P wave is usually obscured in bundle branch block the QRST is also similar but follows a normal sinus P wave after a normal or slightly prolonged P R interval If the pacemaker is above the bundle of His and there is complicating bundle branch block the QRS complex may simulate that of an idioventricular pacemaker

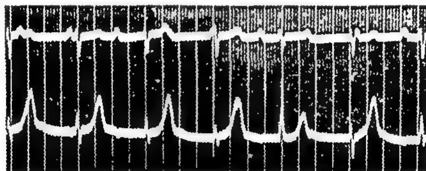


Fig 87 A v dissociation with interference beats Leads III and IV taken simultaneously Atria responding to sinus and ventricles to a v node at slightly different rates (a v dissociation) P R relationship constantly changing After four ventricular responses to the a v node the ventricle responds to a sinus impulse (interference beat) and shows a different (normal) configuration

Prolonged idioventricular rhythm arising in a center in the ventricles below the main bundle rarely occurs in humans as an escape rhythm On the other hand ventricular foci may gain control of the heart as a result of

factors which so increase the irritability of the ventricular conduction tissue that its rate of impulse formation exceeds that of the sinus or a v nodes The resulting rhythms are discussed under ventricular tachycardia–flutter–fibrillation

PREMATURE BEATS

Premature beats or extrasystoles are cardiac contractions of ectopic origin which occur earlier than expected in the dominant or usual rhythm [15] The activating impulse may be in a ventricular focus (causing *ventricular premature beats*), or above the bifurcation of the bundle of His (causing *supraventricular premature beats*) Supraventricular premature beats may arise in the atrioventricular node (nodal premature beats), elsewhere in the atria (atrial premature beats), or rarely in the 'tail' of the s-a node instead of normally in its "head" (sinoatrial premature beats) [30]

Premature beats form the commonest of the cardiac arrhythmias and ventricular premature beats occur much more commonly than those arising in the a v node or elsewhere in the atria

The premature beats may occur irregularly and in isolated fashion or they may occur regularly with respect to each other and to the normal beats When irregularities recur in regular fashion they are termed allorhythms When a normal beat followed by an extrasystole recurs seriatim we term the rhythm *bigemini* or *coupling* Coupling is induced by two beats in close proximity followed by a relatively longer 'compensatory' pause The commonest type of coupling is due to alternate extrasystoles and often caused by digitalis [70] Bigemini may also result from partial a v block (p 385) in which every third beat is dropped from sinus pauses every third beat and from 3 2 sinoatrial block (p 383) (For a detailed discussion see Parsonnet et al)[83] In similar fashion trigemini denotes a grouping of beats in threes formed either by a normal beat and two successive premature beats or by two normal beats followed by one premature beat Similar rhythms may result from partial heart block in which every fourth beat is blocked sinus pauses every fourth beat, and 4 3 sinoatrial block It is essential that these rhythms be checked by listening at the apex of the heart, because premature beats may be too weak to produce a palpable pulse at the wrist

Mechanism of Premature Beats

Premature beats are believed to arise when an ectopic focus in the heart becomes so irritable that its rate of impulse formation exceeds that of the sinus node The impulse arising in the ectopic focus spreads radially in all directions and activates the atria or ventricles This concept explains the experimental production of extrasystoles by direct electrical, chemical thermal or mechanical stimulation of local portions of the heart Similar artificial stimuli have been utilized to evoke premature beats in the human heart exposed during operation [3] Stimulation of the vagus and sympathetic nerves has induced extrasystoles in dogs [68] There is also evidence that the higher centers such as the hypothalamus and possibly the cortex control the spinal sympathetic accelerator centers, stimulation of the posterior hypothalamus has elicited premature beats in cats [10] Premature beats in animals observed during chloroform and other types of anesthesia are probably mediated through sympathetic nerves Certain drugs such as digitalis, epinephrine ephedrine and barium chloride can evoke extrasystoles probably directly by increasing neuromuscular irritability as well as indirectly by stimulating the autonomic nerves to the heart Reduction in extracellular or intracellular potassium predisposes to premature beats especially in patients receiving digitalis therapy (p 267)

Several theories have been proposed to explain the exact mechanism by which extrasystoles arise

1 One of these assumes that a single irritable focus in the heart muscle (or multiple foci) develops emits rhythmic stimuli with greater frequency than the normal pacemaker, and occasionally frequently or continuously gains domination of the cardiac rhythm [48] Whenever this new pacemaker can release an impulse which finds the heart muscle not refractory, it produces a premature beat

2 The fact that premature beats often follow the preceding normal beat at exactly identical intervals suggests that the normal contraction in some way controls the ectopic beat which follows De Boer[8] suggested the theory of reentry to explain this exact coupling According to this concept the sinus impulse activates the heart and causes a cardiac contraction, then reenters the ex

citable ectopic focus of heart muscle by an aberrant pathway and elicits another contraction when the heart muscle is no longer refractory. The coupled extrasystole often occurs during the U wave of the preceding beat, at which time there is a supernormal phase of irritability which would favor the initiation of a premature beat. This might explain the constant time relationship between the extrasystole and preceding beat. Fluctuations in pH are important in predisposing to extrasystoles, perhaps by the effect of the former on the supernormal phase of recovery. The temporary diminution or abolition of extrasystoles and other arrhythmias by hyperventilation may be due to induced alkalosis.[75] According to experimental observations of de Boer[9] on the frog's heart, the mechanism responsible for premature beats, like that causing atrial flutter and fibrillation, is not that of rhythmic impulses from a punctate focus but the reentry of an impulse into a circus ring of muscle tissue (p. 351). This theory could explain the cases of bigeminy due to ventricular premature beats, e.g., those due to digitalis intoxication, in which there is usually a fixed coupling in time relationship between normal and premature beats.[69]

3. A third theory, based on the observations of Kaufmann and Rothberger[35] is that of *pararrhythmia* or *parasystole*.[9] According to their concept, abnormal beats (parasystoles) result from the interaction of two foci concurrently initiating impulses at different rates. As a rule, one of these is the normal pacemaker, the sinus node. The other or ectopic focus is responsible for an independent rhythm prevailing side by side (para) with the sinus rhythm. This ectopic site does not respond to the sinus impulse but continues to form its own stimuli which effect a ventricular response whenever the ectopic stimulus falls outside of the refractory period. These rhythms work independently of each other and the sinus and parasystolic beats bear no constant time relationship to each other, unlike the two rhythms in interference dissociation (p. 330) or in many types of extrasystoles in which the sinus and ectopic beats are coupled at fixed intervals.

The parasystolic focus emits impulses which are characterized by absolute regularity, the cycles of which vary less than 0.01 second, in contrast with the sinus impulses which are more variable. In paroxysmal tachycardia (p. 344), which is explained by a similar mechanism, the absolute equality of cycles between beats is apparent. But Kaufmann and Rothberger[35] also showed that if extrasystoles precede or follow a paroxysm of tachycardia, the interval between such isolated extrasystoles is a mathematically exact multiple of the interval between beats of the tachycardia. Of course, many of the ectopic impulses are ineffective because of the refractory state of the muscle which has just responded to a normal sinus impulse. Local blocks to the dominant sinus impulse (entrance block) are assumed to protect the ectopic center and its impulses from being inactivated.[38] Rarely, the rate of impulse formation in the ectopic focus is more rapid than in the sinus node; in such instances some of the outgoing ectopic impulses are blocked from interfering with the sinus impulses (exit block).

In an analysis of ventricular premature beats which gave rise to temporary bigeminal rhythm, Langendorf and associates[48] divided such bigeminy into two major groups. The first consisted of ectopic beats with *fixed coupling* during grossly irregular dominant rhythm, e.g., atrial fibrillation. In this group the extrasystoles occur when the ventricular cycles are long, whereas short cycles tend to preclude their occurrence. This was explained on the basis of a reentry mechanism of the premature systoles. The second group[45] consisted of ectopic beats with *varying coupling* during a regular dominant rhythm. This was explained by either parasystole or reentry, and the intermittency of the bigeminy was attributed to simple interference or to a disturbance in conduction of a parasystolic or of a reentrant impulse. Miller and Antonius[66] described a case of unusual bigeminal ventricular rhythm in the presence of atrial fibrillation with complete atrioventricular block. The ventricular rhythm was controlled by two ventricular foci alternately producing sequences of an extrasystolic and automatic beat.

It is probable that the premature beats or extrasystoles which are so termed on the basis of their clinical and electrocardiographic features are not all due to the same cause. In particular, a distinction must be made between those extrasystoles which bear a fixed time relationship to the preceding beat and those which are independent of the

basic rhythm The former are probably released by an extraneous stimulus reaching an irritable focus rather than by stimuli originating independently at the ectopic focus [illegible] *Those extrasystoles which bear no constant time relationship to the sinus rhythm but which recur with unchanging rhythm, are best explained by the theory of parasystole*

The Electrocardiogram in Premature Beats

The electrocardiogram differs with regard to atrial, atrioventricular or nodal and ventricular premature beats

Atrial Premature Beats An atrial complex and a ventricular complex occur earlier than anticipated (Fig 68) The P wave is usually abnormal in conformation because the origin and course taken by the ectopic impulse are different from the normal However the P wave is always present although difficult at times to identify When the ectopic impulse arises very close to the sinoatrial node or in its "tail" the P wave is similar in appearance is very far from the sinoatrial node or if the premature beat occurs very early in the atrial recovery period before complete recovery from the preceding atrial contraction

The *QRST* complex appears virtually normal, i e similar to the QRS of the basic rhythm in the same lead For after the ectopic impulse has traversed the atrium, its course in the conduction system of the ventricle is identical with that of a normal sinus impulse However although the QRS *of an atrial extrasystole resembles the normal,* its amplitude is often altered and its conformation is slightly different (aberration of the QRS complex), perhaps due to a slight disturbance in bundle branch conduction or slight refractoriness of the ventricular muscle Sometimes the QRS is so altered (slurred notched and widened) that it resembles that of a ventricular premature beat The aberration often manifests itself only in one bundle usually the right, causing the configuration of

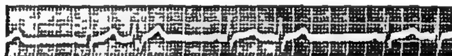


Fig 68 Premature atrial beats A woman aged 47 without organic heart disease Lead I Second ventricular complex is a nodal extrasystole with inverted P following RS. Fourth ventricular complex is an atrial premature beat with a compensatory pause Note coupling effect or bigeminy

to the normal P of the basic rhythm and its direction is the same in each lead as the normal P wave When the ectopic impulse arises low in the atrium its direction is usually retrograde toward the s a node In this circumstance P_2 and P_3 are inverted because the direction of the atrial depolarization process is opposite to the normal as it affects leads II and III However P_1 may be upright isoelectric or inverted depending on the degree *to which the ectopic impulse conforms to the* normal right to left direction (of the sinus impulse) Sometimes premature beats briefly separated in time arise from different ectopic foci in the atria (multifocal atrial premature beats) This occurrence is betrayed by differences in form and direction of premature P waves in the same lead

The *P R interval* is usually greater than the minimal normal of 0 12 second because the path of the ectopic impulse to the ventricle is at least as long as that of the normal sinus impulse The P-R interval of the ectopic beat may be abnormally long if the ectopic center a right bundle branch block Refractoriness of the bundle may be physiologic or due to underlying cardiac disease If physiologic the aberrant conduction disappears with increase of the cardiac rate by exercise [9] The height of the T wave may also be altered The degree of prematurity of the atrial premature systole is probably the major factor determining the degree of aberration of the QRS [8] Rarely also the ectopic atrial stimulus occurs so early that *it cannot be transmitted through the a v node* and bundle which are completely refractory or it reaches a refractory ventricular muscle Then the electrocardiogram of the atrial premature beat discloses an abnormal P wave without a following QRS complex This is termed a *blocked premature atrial beat* It differs from heart block in that the P wave occurs prematurely and is usually different in configuration and direction from the P wave of the basic rhythm

The QRST complex of an atrial premature beat is followed by a pause which is slightly longer than the basic T P interval This pro-

longation represents the normal interval between beats plus the interval consumed by the ectopic impulse to travel back to the sino-atrial node. If the P-P interval from the ectopic to the following normal beat is added to the P-P interval between the ectopic and preceding normal beat, it is somewhat less than two normal P-P intervals of the basic rhythm. Thus the T-P pause is longer than normal but not compensatory, i.e., it does not quite restore the dominant rhythm by exactly compensating for the abnormally short T-P interval before the premature beat.

Atrioventricular Nodal or Junctional Premature Beats. The QRS complex occurs prematurely but is usually normal in configuration (supraventricular type), since the nodal impulse follows the normal pathways as it activates the ventricles.

The origin of the premature beat in the a-v node or bundle is indicated by the abnormal position or configuration of the P wave (Fig. 68). The P wave represents either (a) retrograde activation of the atrium by the nodal impulse or (b) normal sinus activation of the atria while the nodal impulse activates the ventricles. In the former circumstance, the P wave is altered in configuration and either precedes, coincides with, or follows the QRS. The ectopic P wave is sharply inverted (V-shaped) in leads II, III and aV_F and upright in aV_R and aV_L. If the atria are activated by the sinus impulse, the P wave is normal in appearance, continues its basic rhythm and may be detected just before, within or after the QRS complex.

With retrograde conduction of the nodal impulse, the P-R interval is less than 0.12 second when it precedes the QRS complex because the pathway from the a-v node to the ventricles is shorter than from the s-a node. The P wave of the nodal extrasystole precedes the QRS when the ectopic focus is in the upper portion of the a-v node, is lost in the QRS when the focus is lower in the node, and follows the QRS when the ectopic focus is in the lowest portion of the a-v node.

Ventricular Premature Beats. The *QRST complex* differs strikingly from the normal because the ectopic impulse takes an abnormal and longer course through the ventricles (Fig. 69A). The QRS is of high voltage, slurred, notched and widened to 0.13 second or more. The T wave is altered secondarily. It is usually directed opposite to the QRS, and is wide and tall. Often the T wave is deformed by a P wave. The P wave, although present, is usually partially or completely obscured by the QRST complex. The ventricular premature beat is distinguished from supraventricular premature beats by the bizarre contour of the QRST complexes and by the absence of premature ectopic P waves. The occasional supraventricular premature beat with bizarre QRST (supra) is associated with an ectopic P wave which is usually very premature.

The ventricular extrasystole is followed by an abnormally long pause (T-P interval) preceding the subsequent normal sinus beat. Usually, the ectopic ventricular impulse is not conducted retrograde to the atria and the latter are activated at their normal time by the sinus impulse. Since the dominant sino-atrial rhythm is undisturbed, the normal P and QRS which follow the extrasystole also fall at their expected time. The pause after the extrasystole is therefore really compensatory (Fig. 69B). And the P-P interval between the normal beat preceding and the normal beat following the extrasystole is exactly twice the P-P interval between uninterrupted normal beats. Slight variations may be due to sinus arrhythmia. The T wave in sinus beats following ventricular extrasystoles may be inverted although other sinus beats have an upright T wave. Mann and Burchell[4] found heart disease present in 93 per cent of 46 patients who had inverted T waves following extrasystoles, whereas in a control group in which the post-extrasystolic T wave was upright, heart disease was present in only 57 per cent of cases.

Occasionally, however, the ectopic ventricular impulse is conducted retrograde and activates the atria as well as the ventricles. According to the studies of Kistin and Landowne[44] with esophageal electrocardiograms, such retrograde conduction is common and was demonstrated in 15 of 33 unselected individuals with ventricular premature beats. Retrograde conduction may be documented electrocardiographically by inverted P waves in leads II and aV_F following the bizarre QRS of the ventricular extrasystole. Occasionally a fusion P wave occurs when a retrograde ventricular impulse combines with an antegrade sinus impulse to activate the atria.

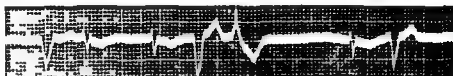
Site of Origin of Ventricular Premature Beats. The electrocardiogram permits a differentiation between premature beats arising

in the left or right ventricles and probably also between those arising at the apex base or near the septum These distinctions are based on electrocardiographic records made while ventricular premature beats were induced by electrical stimulation of human hearts exposed during operations for pericarditis

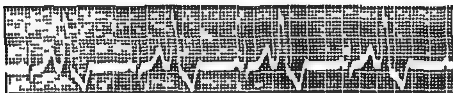
It is now generally believed that the electrocardiographic configuration of left and right ventricular extrasystoles is exactly opposite to that formerly depicted on the basis of experi-

Apical ventricular extrasystoles are usually characterized by bizarre QRS complexes with main deflection downward in all three leads

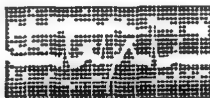
Septal ventricular extrasystoles are characterized by QRS complexes which hardly differ from the normal because the ectopic impulse, like supraventricular impulses, reaches both ventricles almost simultaneously The QRS may be slurred, notched and of very low voltage in lead I



A



B



C

Fig 69 A Premature ventricular beats of multifocal origin Lead II Abnormal configuration of QRS First arises from impulse in left ventricle fifth from right ventricle P waves hidden in ventricular complexes

B Premature ventricular beats causing bigemini or coupling in a boy aged 7 with a normal heart Lead II Compensatory pause after each premature beat

C Interpolated premature ventricular beat A man aged 75 with atherosclerotic heart disease Lead I The second ventricular complex is a premature beat interpolated between two normal beats There is no compensatory pause the following normal beat coming at its regular time

mental observations in dogs[49, 69] (See also discussion under bundle branch block p 397) *Right ventricular extrasystoles* are characterized by slurred notched and widened QRS complexes with the main deflection (i e the deflection of greatest duration) upward in lead I and usually downward in lead III Conversely *left ventricular extrasystoles* have the main deflection of the bizarre QRS complex downward in lead I and usually upward in lead III

Basal ventricular extrasystoles are usually characterized by bizarre QRS complexes with main deflection upward in all three leads

It should be noted that the localization of various premature beats may not correspond to the above description when the extrasystoles arise near the dividing line between the left and right ventricles and between base and apex The position of the heart in the chest wall may modify the electrocardiographic conformation of right and left ventricular extrasystoles[44, 49]

When premature beats in a given electrocardiographic lead are seen to arise from different sites as indicated by the direction of the QRS complex they are termed multifocal extrasystoles or bidirectional extra

systoles They are often indicative of digitalis intoxication or of severe myocardial disease

Interpolated Premature Beats The term extrasystole used synonymously with premature beat is misleading in that there is actually no extra beat, the precocity of the premature beat being compensated by the subsequent pause before the next normal sinus controlled ventricular contraction The premature ventricular contraction merely takes the place of a normal sinus ventricular contraction which fail to appear because the ventricles are refractory But occasionally when the heart rate is slow, a premature beat may occur so early in diastole that it is completed in time to permit the next sinus impulse to elicit a ventricular contraction Here the premature beat is added between two normal beats in their normal rhythm and is actually an *interpolated extrasystole* (Fig 69C) The normal beat after the extrasystole may be slightly delayed and its P R interval prolonged due to a partially refractory state of the conduction system The normal beat after the interpolated extrasystole is usually a small contraction due to incomplete filling in the brief diastole between the extrasystole and following contraction The extrasystole itself produces no pulse wave because it occurs so early in diastole that ventricular filling is minimal

Etiology of Premature Beats

The clinical causes of premature beats are uncertain as there is no direct evidence of mechanisms identical with those which induce extrasystoles in the experimental animal (p 332) It is probable that premature beats in man may follow stimuli which reflexly stimulate the vagus and sympathetic nerves e g the premature beats occasionally induced by painful stimuli carotid sinus pressure breath holding or forced respiration and perhaps others of less certain origin

In clinical practice the majority of patients with premature beats are not found to have organic heart disease [30] ■ On the other hand the presence of heart disease has a distinct tendency to increase the occurrence and frequency of premature beats Atrial premature beats tend to occur in association with disease or enlargement of the atria e g in cases of mitral stenosis or cor pulmonale In noncardiac patients premature beats usually appear without apparent cause but they sometimes seem to be related to emotional stress and conflict [81] mental or physical fatigue irregular sleep and digestive disturbances especially when these are combined with excessive smoking or drinking of alcohol or coffee But the relationship is obscure in that only certain individuals are susceptible to premature beats when exposed to the above factors and the same individual does not always respond with premature beats to apparently identical stimuli

Premature beats have been noted in patients with biliary and renal colic as well as with chronic disease of the biliary tract A causal relationship is unproven Infections of various types especially when associated with fever have been said to favor the development of premature beats but without strong evidence Premature beats have been recorded as being related to cerebral lesions ■ Atrial and ventricular premature beats occur with very high frequency during cardiac surgery as a result of manipulation of the heart or neighboring structures and during cardiac catheterization [3, 83, 28, 11] The occurrence of premature beats is so frequent that a causal relationship to any given factor is often difficult to prove or exclude

Age Premature beats occur at all ages but rarely in infancy and childhood They have been heard during auscultation of the fetal heart sounds and confirmed by electrocardiograms taken immediately after birth After the age of 50 the frequency increases notably and after 70 premature beats occur intermittently in almost all individuals

Symptoms of Premature Beats

Most persons with premature beats are unaware of their presence But often there is a momentary, more or less disturbing local discomfort in the precordium The greatest discomfort has usually been attributed to the long compensatory pause after the premature beat or to the strong contraction that follows But Kline and Bidder[42] demonstrated that the disagreeable sensation was due to the premature beat or the compensatory pause and Ungerleider and Gubner[81] indicted the *premature beat* alone as the cause of discomfort

There may be a sensation of stoppage of the heart momentary faintness or dizziness and intense associated anxiety The normal beat after the premature contraction is experienced as a strong thump against the chest wall as the ventricle expels its unusually large content accumulated during the long diastolic

pause The entire sequence of extrasystole, long pause and strong beat produces an irregularity which evokes a distressing heart consciousness or palpitation which may be described as an oppression, fluttering thumping skipped beats, or a sinking feeling Occasionally the discomfort is localized in or radiates to the neck where the patient experiences a fullness, tightness pulsation or *wave reaching to the top of the head This* may be caused by the regurgitant stream from the right atrium to the neck veins when the atrium contracts simultaneously with the ventricle and the tricuspid valve is shut

When runs of extrasystoles occur, general symptoms such as anxiety pallor, sweating nausea, weakness dizziness faintness and breathlessness may ensue It is often difficult to determine to what extent these symptoms are of psychic or of circulatory origin There may be distinct pain simulating that of angina pectoris

Premature beats often become annoying when the patient is at rest and apparently relaxing especially when he retires for the night It is uncertain whether slowing of the heart rate at such times predisposes to their appearance or whether the absence of other distractions makes the patient more aware of their *existence Conversely exercise often seems to* eliminate the premature beats In fact they are often eliminated at least temporarily by any factor which increases the heart rate e g exercise atropine, nitrites In some patients however especially in patients with organic heart disease premature beats are induced by exercise

Physical Signs of Premature Beats

Auscultation of the heart detects the premature beat which occurs too early in the cardiac cycle and is followed by a longer pause than normal The premature beat may be similarly recognized at the pulse but often the premature contraction is too weak to produce a palpable pulse wave

Both sounds of the premature contraction are usually audible but only the first sound may be heard if the ventricular contraction is too slight to open the semilunar valves The extrasystolic heart sounds may be dull and almost inaudible if the ventricle contracts when it is very incompletely filled or more often there may be a sharp snapping first sound By a simultaneous phonocardiographic and electrocardiographic study, Cossio et al[14] found that in 15 of 16 patients with atrial extrasystoles, the first sound of the extrasystole was always louder than the first sound of the preceding or following normal systole In cases of ventricular premature beats, the first sound was usually louder but occasionally of normal or diminished intensity When the first sound of the extrasystole was louder it *was also delayed in onset relative to the onset of the QRS The increased intensity and de*layed onset depend on the degree of prematurity and the consequent position of the a v cusps With premature contractions the a v cusps are lower than normal at the onset of ventricular contraction More time therefore elapses before the valve is closed and this is associated with increased motion increased vibration and increased intensity of sound Splitting of the first sound is due to asynchronous contraction of the ventricles which occurs only with ventricular premature beats This asynchronism accounts also for the lower incidence of intensified first sounds with ventricular extrasystoles

Diagnosis

Premature beats are usually recognized easily by auscultation and less regularly by palpation of the radial pulse Sometimes they *occur so infrequently* that they are absent at the time of physical or electrocardiographic examination but their occurrence may be suspected from the patient s description

The electrocardiogram is essential for definite diagnosis and localization of premature beats (p 334) Ventricular extrasystoles are usually distinguishable from atrial or *nodal extrasystoles by the widening notch*ing and slurring of the QRS in the former and the relatively normal QRS complex in the latter two The P wave in atrial premature beats precedes the QRS the P R interval is normal and the T P pause is longer than normal but not compensatory The P wave in nodal premature beats is inverted in leads II and III may follow be fused with or precede the QRS complex But if it precedes then the P R interval is abbreviated to less than 0 12 second Rarely upright P waves in leads II and III were observed in a case of lower a v rhythm[15]

Clinical differentiation between atrial nodal and ventricular premature beats is extremely difficult but may be successful

based on the following observations Ventricular extrasystoles are followed by a compensatory pause which permits the next beat to occur at the same time as if there had been no premature beat On the other hand the pause after an atrial extrasystole is incomplete and the following normal beat occurs too early in the basic rhythm as may be determined by meticulously and rhythmically counting and tapping with a pencil or with the foot A striking systolic a pulsation in the neck may accompany a nodal or ventricular extrasystole instead of the normal systolic collapse since the atrium may contract at the same time that the tricuspid is closed by the nodal or ventricular extrasystole Interpolated extrasystoles may be suggested by the occurrence of three beats in rapid succession in the time normally occupied by two and without a long pause In trigeminy three beats in rapid succession are followed by a long pause

When multiple premature beats recur frequently they may be confused with atrial fibrillation on clinical examination The rate of the latter is usually rapid (120 or more) unless the patient has been digitalized Increase of the heart rate by exercise or the administration of nitrites will often eliminate the extrasystoles but not atrial fibrillation Careful auscultation discloses that the long pauses in extrasystoles are preceded by a premature beat with atrial fibrillation there are pauses without preceding premature beats The electrocardiographic distinction is simple

Extrasystolic bigeminy may be distinguished from cardiac alternans (p 146) by auscultation which reveals even spacing in time in alternans while there are briefer and longer intervals in bigeminy

Sinus arrhythmia and heart block may produce an irregularity resembling frequent premature beats Electrocardiographic study is desirable for differentiation Careful auscultation discloses that the irregularity in sinus arrhythmia is one of increasing and diminishing frequency of beats often related to the phases of respiration and may be abolished by exercise (p 325) In heart block there is usually a bradycardia and the irregularity is not characterized by premature beats which are always followed by a long pause

Prognosis

As a rule premature beats are of no clinical importance They appear in isolated fashion at infrequent intervals and produce minimal momentary symptoms or none at all They are usually unaccompanied by organic heart disease When heart disease is present its diagnosis and prognosis should be based on findings independent of the extrasystoles According to Berliner and Huppert[4] benign ventricular premature systoles are associated with a narrower QRS than those accompanying organic heart disease extrasystoles with a QRS wider than 0 16 second were considered to suggest the probability of organic heart disease The presence of premature beats per se without associated heart disease rarely has significance as to longevity or as to suitability for life insurance military service or employability Occasionally the frequency of the extrasystoles or the anxiety associated with their occurrence produces symptoms of a severity out of proportion to their prognostic unimportance

Atrial premature beats may be clinically more important because of the greater likelihood of underlying heart disease Their presence should initiate an especially careful search for rheumatic heart disease with mitral stenosis In patients known to have mitral stenosis they may represent harbingers of impending atrial tachycardia flutter or fibrillation However even atrial premature beats are not of serious prognostic significance when there is no underlying heart disease

Ventricular premature beats are often of serious import when they are multifocal i e when they come from several different sites in both ventricles as seen in a given lead of the electrocardiogram This finding may denote advanced myocardial disease and impending ventricular tachycardia or fibrillation But it may also be indicative of reversible myocardial irritation due to digitalis intoxication Extrasystoles forming bigeminal rhythm are commonly due to digitalis intoxication When they occur with small doses of digitalis they are said to imply an unfavorable course

TREATMENT

General Measures

Premature beats are usually asymptomatic and require no treatment When as is often the case the extrasystoles are first discovered on routine examination and are unknown to the patient attention should not be directed to their presence However in ex

ceptional circumstances it may be preferable to state their presence and explain their insignificance if it is likely that the patient will see some other physician who may alarm him. If the patient is aware of their occurrence no treatment is usually necessary except convincing the patient that he has no heart disease. In the absence of heart disease the patient may receive special encouragement if he is told that none of his activities need be restricted. Whether or not heart disease is associated, the patient sometimes needs assurance that nothing dire will eventuate.

Treatment is indicated when the symptoms due to the extrasystoles are distressing despite reassurance. Possible irregularities in hygiene should be corrected even if no definite causal relationship can be proven. The patient should obtain adequate sleep and sufficient periods of both relaxation and simple exercise. Constipation should be corrected. The diet should consist of bland, easily digestible foods and the caloric intake should be diminished if the patient is obese and has been gaining weight. A cholecystectomy or dietary correction of symptoms due to disease of the biliary tract or peptic ulcer may be followed by disappearance of the premature beats. Emotional stresses should be eliminated if possible. Sometimes a vacation with change of environment may be necessary and helpful. Sedatives such as phenobarbital, chloral hydrate or bromides may be beneficial.

Aside from these general measures, it is advisable to eliminate smoking, alcohol and coffee completely at least for a reasonable test period. If the premature beats disappear or become tolerable, resumption in moderation may be tried if desired. When premature beats occur in bigeminal or multifocal form during digitalis therapy, digitalis should be discontinued.

Specific Drug Treatment

The most effective specifically antiarrhythmic drugs in the treatment of premature beats are procaine amide (chiefly for ventricular extrasystoles), quinidine and potassium salts (chiefly in digitalis induced extrasystoles). Occasionally digitalis abolishes premature beats.

Procaine Amide (Pronestyl). Procaine amide has been found to be effective in the treatment of various cardiac arrhythmias especially ventricular premature beats and ventricular tachycardia.[39, 46, 59, 83] In my experience it is more effective than quinidine in the prevention and treatment of ventricular premature beats.

Procaine amide differs structurally from procaine in that para aminobenzoic acid and diethylaminoethanol are bound through an amide (NH) linkage instead of an ester linkage as in procaine. It is not affected by the procaine esterase of the body and is therefore more stable. Hence therapeutic levels can be readily maintained. It is effective by the oral route as well as by intramuscular or intravenous injection. It produces much less central nervous stimulation than procaine.

Myocardial Action. Procaine amide acts, like quinidine, by depressing myocardial excitability.[65] It is presumed to raise the ventricular threshold to stimulation, to prolong ventricular conduction and possibly to increase its refractory period. It has a similar action on atrial muscle but to a lesser degree. Hemodynamic studies[64] indicate that procaine amide reduces the cardiac output and the pulmonary artery pressure and slows the velocity of the blood flow.

Administration and Dosage. To abolish and prevent the recurrence of premature beats Pronestyl is given orally in an initial dose of 0.75 to 1.25 gm. followed by 0.5 gm. (2 capsules each 250 mg.) at four to six hour intervals, i.e. four to six times daily. When the extrasystoles are controlled the dose is progressively reduced to 0.5 gm. four times daily or three times daily. Finally a maintenance dose of 0.25 gm. four times daily is usually adequate. If this initial schedule is ineffective, 1 gm. doses may be given at four hour intervals until the extrasystoles are controlled or there are toxic symptoms. Usually a peak plasma level is attained with this dose in one hour and this level declines to minimal levels in four to six hours. Thus a cumulative effect is obtained when the drug is administered in doses of 0.5 to 1.0 gm. at four hour intervals or oftener, and frequently also when administered at six hour intervals.

Because of possible toxicity of Pronestyl patients taking the drug over a continuous period of time must be checked by repeated blood counts and electrocardiograms.

Toxic Effects. *Electrocardiographic changes* may occur similar to those produced by

quinidine *Widening of the QRS complexes* is a characteristic toxic effect Caution is indicated when the QRS complexes are prolonged beyond 0 14 second *Ventricular tachycardia* is occasionally induced and rarely ventricular flutter or fibrillation [13, 19, 25] Less striking electrocardiographic changes not necessarily toxic include prolongation of the Q T interval diminished voltage of the QRS complexes lowering or inversion of the T wave, slight prolongation of the P R interval and electrical alternans

Gastrointestinal symptoms especially anorexia nausea or vomiting are not uncommon But these are likely to occur only with larger doses such as 4 gm or more daily These symptoms rarely require discontinuation of the drug except temporarily As a rule the symptoms will not reappear if smaller doses of the drug are resumed

Agranulocytosis is very uncommon but one of the most serious complications and has been fatal in some cases [33] Usually it occurs after prolonged oral medication

Hypotension is a serious complication of Pronestyl only when the drug is administered intravenously [30, 4] Hypotensive effects after intramuscular or oral administration are infrequent and insignificant [2] Following intravenous administration some degree of hypotension is common depending in part on the dose and speed of administration Fatalities due to shock myocardial ischemia or other reactions may occur especially in patients with severe myocardial disease [4]

Other toxic effects which are relatively rare include headache drowsiness mental symptoms or psychoses urticaria chills and fever [1] or profuse sweating

Quinidine Sulfate (See also p 365) This acts by depressing myocardial excitability One may begin with an initial test dose of 0 2 gm (3 grains) followed by 0 3 to 0 6 gm (4½ to 9 grains) three to six times daily for a trial period of a week If desired these dosages may be attained by progressive increases If the extrasystoles disappear a maintenance dose may be determined by gradual reduction of the dose Eventually it should be discontinued Sometimes digitalis in doses of 0 1 gm three times daily for three days followed by 0 1 gm daily is effective whether or not heart failure is present and even when quinidine has failed

Potassium Salts Potassium chloride phosphate or acetate is often effective in controlling extrasystoles especially those due to digitalis toxicity [11, 7] The dosage is 2 to 4 gm (30 to 60 grains) three or four times daily dissolved in a 25 per cent solution and suitably flavored [7] or it may be given in tablet form For intravenous administration potassium is available in ampules containing 3 7 gm or 50 mEq of potassium chloride The contents are dissolved in 500 or 1000 cc of 5 per cent glucose in distilled water and administered by intravenous drip in not less than 2 hours Stronger concentrations or more rapid flow usually results in almost intolerable pain along the vein *Potassium salts are contraindicated or should be given with the greatest caution in patients with serious renal impairment*

Magnesium salts have also been found effective in abolishing extrasystolic bigeminy due to digitalis [6, 21] Benemid (Probenecid) administration was followed by disappearance of disabling bigeminal extrasystoles in a case of gout [6] It was presumed that the Benemid abolished an ectopic ventricular focus due to uric acid deposit by increasing the excretion of uric acid

Ambonestyl (2 diethylaminoethyl isonicotinamide) Preliminary reports indicate that this drug administered intravenously in 0 5 gm doses at 10 minute intervals suppresses premature ventricular contractions and bigeminal rhythm [13] It appears to have advantages over procaine amide and quinidine in the absence of depression of cardiac conduction and lack of serious hypotension on intravenous administration These advantages suggested that Ambonestyl might be particularly useful in treating ventricular arrhythmias in patients with conduction disturbances in controlling arrhythmias during anaesthesia and cardiac surgery

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Chapter 14

THE ECTOPIC TACHYCARDIAS

The ectopic tachycardias denote abnormally rapid cardiac rhythms in response to impulses arising outside the sinoatrial node. They are also termed paroxysmal tachycardias because of their frequent occurrence as attacks of cardiac acceleration which start and stop abruptly. They include

1. Atrial (and nodal) paroxysmal tachycardia
2. Atrial flutter
3. Atrial fibrillation
4. Ventricular tachycardia
5. Ventricular fibrillation

Like premature beats these tachycardias are engendered by stimuli which arise in ectopic centers in the atria or ventricles, they are therefore classified as ectopic rhythms. They are distinguished in this respect from sinus tachycardia in which the rate is also rapid but the controlling impulse arises normally in the sinoatrial node. The ectopic focus responsible for premature beats dominates the rhythm of the heart intermittently while that responsible for paroxysmal tachycardia becomes the pacemaker for shorter or longer continuous periods.

The paroxysmal tachycardias are considered separately because it is the rapid heart rate more than any other feature of a cardiac arrhythmia which produces serious circulatory disturbances. As a rule the arrhythmias hardly derange circulatory function and provoke little local precordial discomfort provided the heart rate is slow or normal. Bradycardias, even of intense degree whether regular or irregular are also rarely responsible for circulatory distress unless the interval between beats exceeds 3 seconds. Within a reasonable range a satisfactory circulation is maintained regardless of rate or rhythm, provided there is an adequate interval for myocardial recovery and ventricular (diastolic) filling. On the other hand these essential events become progressively restricted with increasing cardiac rate (p 91).

Ordinarily paroxysmal tachycardias are transient while the dominant rhythm is of sinus origin and the rate is normal. Sometimes runs of atrial, nodal or ventricular systoles termed *repetitive paroxysmal tachycardia*[153, 47] are almost constantly present for months or years and thus become the dominant rhythm while normal sinus rhythm interrupts only transiently. Such paroxysms consist chiefly of atrial tachycardia less commonly of ventricular tachycardia, but also of nodal tachycardia, atrial flutter or fibrillation. Organic heart disease is usually absent. Palpitation, independent of exertion dyspnea and syncopal attacks are the commonest symptoms. The prognosis is good and the paroxysms in children disappear during adolescence. Those in adults tend to subside spontaneously. Drug treatment is usually ineffective.

Rare cases of *chronic atrial tachycardia*[47] have been distinguished from repetitive atrial tachycardia by the absence of periods of sinus rhythm in the former. Chronic atrial tachycardia may be associated with varying degrees of atrioventricular block and a ventricular rate between 120 and 180 per minute. This arrhythmia is refractory to treatment but digitalis is useful to slow the ventricular rate.

ATRIAL PAROXYSMAL TACHYCARDIA

This is the common form of recurrent palpitation associated with very rapid but extremely regular heart rates.[113] Atrial paroxysmal tachycardia is observed many times as frequently as ventricular tachycardia. A distinction between paroxysmal tachycardias initiated in the a v node and those initiated elsewhere in the atria is often extremely difficult or impossible.

Mechanism

It has been assumed that atrial paroxysmal tachycardia like atrial extrasystoles results from a rapid succession of rhythmic impulses arising in an irritable ectopic focus in the

atrium[1,7] Transitions from atrial extrasystoles to atrial tachycardia are sometimes seen in the same electrocardiograms and the configuration of the complexes is identical in both arrhythmias The possibility also that this ectopic focus is a parasystolic center protected by local blocks has been suggested by advocates of the theory of parasystole (p 333) More recently the theory of circus rhythms generally invoked to explain atrial flutter and fibrillation (p 351) has been expanded to apply also to atrial paroxysmal tachycardia The evidence for this belief has been summarized by Barker Wilson and Johnston[11] who suggested that atrial paroxysmal tachycardia is due to a special kind of circus rhythm (reentry) which involves the sinoatrial or the atrioventricular node in its pathway But curves of the momentary atrial electrical axes suggest that the atrial tachycardia unlike flutter and fibrillation is not due to circus movements[84] An essential distinction is the separation of the atrial deflections by isoelectric intervals in atrial tachycardia whereas in atrial flutter the electrocardiographic oscillations are continuous and there is no isoelectric interval between P waves But Prinzmetal et al[137] have stressed that the undulatory pattern of atrial flutter is dependent in large measure on the atrial rate and is not present in all leads or in borderline cases and that there is not a fundamental difference between atrial flutter and tachycardia

The atrial rate varies usually between 140 and 220[113] per minute but most commonly between 180 and 200 Occasionally the atrial rate is as high as 300 per minute The ventricles almost always respond to each atrial beat But several series of cases have been collected in which there was an associated atrioventricular block usually 2 1[83] Paroxysmal atrial tachycardia with block has been noted occasionally as a result of digitalis intoxication especially with deficient potassium[70, 134] and in association with posterior myocardial infarction[137] Paroxysmal tachycardia may be associated with bundle branch block and occasionally as a result of digitalis toxicity with bidirectional aberrant ventricular complexes suggesting alternate conduction down the left and right bundle branches [4, 100] In infants atrial paroxysmal tachycardias occur in which the atrial rate is as high as 300 per minute and yet there is a 1 1 ventricular response[107, 205] The usual atrial rate of 140 to 220 in paroxysmal atrial tachycardia compares with an atrial rate of 250 to 350 in atrial flutter and 400 to 600 in atrial fibrillation The progressively greater frequency of a v block in the latter two conditions is explainable by the more frequent atrial impulses attempting to traverse the a v node and bundle and probably also by some impairment in atrioventricular conduction in atrial flutter and fibrillation

The Electrocardiogram

The characteristic feature is a rapid regular series of ventricular complexes (RT waves) with the T wave slightly modified by fusion with the P wave (Fig 70) The QRS complex is usually of relatively normal contour but in prolonged paroxysms especially with ventricular rates exceeding 200 per minute the QRS may become widened notched and slurred due to impaired intraventricular conduction

The P waves though present are difficult to identify because the abbreviated interval between beats causes them to fuse with the preceding T When only QRS complexes are apparent atrial tachycardia cannot be distinguished from nodal tachycardia When identified the P waves in limb leads I and II are usually upright and relatively normal in contour suggesting that the atrial impulse originated in the cephalic portion of the atrium near the sinoatrial node Occasionally the P waves may be inverted in leads II and III suggesting an origin in or near the a v node In nodal tachycardia the P R interval is abbreviated or the P wave is concealed in or follows the QRS complex Paroxysmal nodal tachycardia may be associated with retrograde heart block reciprocal rhythm and blocked reciprocal beats[35] The P waves in atrial tachycardia may be best identified by taking esophageal leads[3, 38] or a precordial lead from the right side of the sternum[46] e g by placing the exploring chest electrode in the third interspace to the right of the sternum[5] In this manner also the occasional occurrence of a v block (usually 2 1) in atrial paroxysmal tachycardia may be discovered[66] Atrial tachycardia with the Wenckebach phenomenon has been observed during the course of cardiac catheterization[1,1] The T wave is often inverted after an attack of paroxysmal atrial tachycardia but rapidly reverts to normal

The onset of a paroxysm as observed in electrocardiograms, commences abruptly with a preliminary extrasystole its termination is likewise abrupt, a brief pause intervening before the prompt resumption of sinus rhythm

Etiology

The etiology of atrial paroxysmal tachycardia is obscure The same nervous, toxic and digestive disturbances, emotional stress fatigue, exertion and disease of the biliary tract which have been held responsible for premature beats, have also been indicted as responsible for attacks of atrial tachycardia Atrial tachycardia occurs frequently in patients with the Wolff Parkinson White syndrome (p 405) Atrial tachycardia, like other atrial arrhythmias has been observed during cardiac catheterization[143 [illegible]] and cardiac surgery[25] Pregnancy was said to predispose to paroxysmal atrial tachycardia[201] Paroxysmal atrial tachycardia with atrioventricular block may be induced by digitalis[70 134] (p 267) Chronic atrial tachycardia, with slowing of the heart rate and occasional sinus rhythm with recumbency only has been reported[145]

Heart disease is usually absent, but evidence of rheumatic cardiovalvular disease is not uncommon Atrial tachycardia is uncommon in myocardial infarction[9]

Paroxysmal atrial tachycardia occurs at any age, possibly it is most common between twenty and forty [illegible] [134] Its occurrence in infancy and childhood has been reviewed by Nadas et al[148] in a study of 41 cases and by Wright[19] Usually it is discovered in the first four months of life and almost always in boys *It may be congenital,*[3] and cases of paroxysmal tachycardia with onset in utero have been described[215] While the paroxysms *of tachycardia in infants and children are* usually atrial tachycardias they are occasionally atrial flutter and rarely ventricular tachycardias Recurrences are probable during the first year of life but usually not thereafter, unless the child has Wolff Parkinson White syndrome In older children paroxysmal tachycardias affect either sex and in the majority of cases are associated with congenital heart disease or some other etiologic factor Rhabdomyoma of the heart has been found at postmortem examination of some infants who had *suffered from paroxysmal* atrial tachycardia[113]

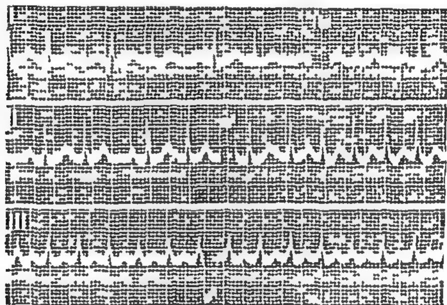


Fig 70 Atrial paroxysmal tachycardia Occasional atrial premature beats in leads I and II preceding onset of atrial tachycardia in lead II and continuing in III Ventricular configuration resembles normal complexes in lead I P and T fused Rate 190 per minute.

Symptoms

The onset is sudden and without warning Often a rapid change in position of the head or trunk an unexpected emotional upset or an unpleasant dream appears to unleash the attack But usually there is no apparent precipitating cause

There may be a sudden thump or two *against the chest wall* a seeming momentary

stoppage of the heart or some other precordial discomfort followed by a continuous palpitation fluttering racing or pumping of the heart beat Sometimes there is definite precordial pain a smothering sensation in the chest and throat fullness or a sense of pulsation in the neck and head or epigastric distress However there may be only mild palpitation or no symptoms at all especially with relatively slow ventricular rates or with paroxysms of brief duration

These *local symptoms* are often overshadowed by *psychic and reflex nervous* manifestations especially when the attacks persist for more than a few minutes Anxiety or even angor animi weakness or exhaustion coldness or sweating and a sense of smothering may occur early There may be dizziness faintness or momentary syncope at the onset Abdominal distention, gaseous eructations salivation nausea or vomiting may occur Occasionally the vomiting appears to terminate the attack whether the emesis occurs spontaneously or is induced There may be polyuria during or at the termination of the paroxysm

Serious circulatory disturbances may develop if the rate is exceedingly rapid but especially if there is underlying cardiac disease and if the paroxysm is prolonged Although physiologic experiments indicate that acceleration of the heart beyond 180 per minute progressively reduces the cardiac output it is remarkable how often heart rates over 200 per minute are tolerated for many hours or even days without evidence of circulatory insufficiency provided the heart is otherwise normal But in hearts with serious organic disease prolonged tachycardia is very likely to induce failure especially pulmonary edema

Weakness pallor perspiration and coldness of the extremities may be due to a diminished cardiac output The clinical picture of shock with extreme hypotension may develop Cerebral ischemia may be responsible for faintness or syncope In extreme degree peripheral slowing of the circulation is followed by thrombosis and gangrene of an extremity

Symptoms and signs of congestive heart failure may also develop These include dyspnea and cough due to left ventricular failure Occasionally there is a frothy blood stained sputum indicative of pulmonary edema The patient s veins may become engorged and his pallor suffused with cyanosis The liver may enlarge and the abdomen become painful and tender The attack may occasionally terminate fatally, either with signs of progressive failure or suddenly As a rule however the paroxysm ends abruptly normal rhythm is restored and the symptoms and signs of circulatory insufficiency abate rapidly

The occurrence of pain has been mentioned Occasionally the pain closely resembles the compressing substernal pain of angina pectoris or cardiac infarction It may actually be due to functional coronary insufficiency and myocardial anoxia secondary to the tachycardia

The *paroxysmal supraventricular tachycardia in infants* is characterized by a cardiac rate of 150 to 300 in one instance 305 per minute[15] Although it may be asymptomatic and is often unrecognized[16] there is usually failure to eat fretfulness or drowsiness vomiting pallor or cyanosis tachypnea fever and leukocytosis Congestive heart failure may result when the tachycardia is prolonged but cases of atrial tachycardia persisting for years with rates of 150 to 200 have been reported without clinical evidence of heart failure[17] In the presence of heart failure cardiac and hepatic enlargement are the prominent findings Pneumonia is often diagnosed instead of heart failure but both pneumonia and heart failure may be present

Signs

Physical examination usually reveals only the regular rapid heart rate The rate remains mathematically constant despite changes of position emotion or exercise[11] The heart sounds may present a tic tac rhythm (embryocardia) The heart is usually normal in all other respects However cardiac enlargement and murmurs may disclose underlying heart disease Sometimes enlargement develops only with the occurrence of heart failure this is reversible with restoration of normal rhythm Murmurs previously present such as that of mitral stenosis may disappear during the tachycardia Therefore examination at that time may not reveal the underlying disease

In severe and prolonged attacks the patient may appear obviously anxious or agitated and there may be objective signs of congestive failure

The pulse is very rapid and small but regular However, since the pulse may be very

deceptive as to regularity or irregularity this quality should always be determined by cardiac auscultation

There may be a prominent and even palpable pulsation of the cervical veins

The blood pressure often falls during severe or long paroxysms Under these circumstances the systolic pressure drops more than the diastolic with a resulting fall in pulse pressure

Diagnosis

See page 378 for diagnosis and differential diagnosis of the tachycardias

Prognosis and Course

Paroxysms of atrial tachycardia stop as abruptly as they begin either spontaneously or because the patient adopts certain positions takes a deep breath holds his breath with glottis closed or because the physician controls the attack As a rule, the attacks subside spontaneously in seconds or minutes, but attacks with disturbing symptoms last for several hours and occasionally for several days They are distinguished from attacks of atrial flutter which may persist for many days weeks or even months (chronic atrial tachycardia)[107] However the attacks of paroxysmal tachycardia which are associated with atrioventricular block often last for many hours or days and occasionally for weeks months or even years[113]

In most cases paroxysmal atrial tachycardia is of no clinical importance either from the viewpoint of producing disturbing symptoms or of denoting the presence of organic heart disease The paroxysms may occur rarely at long intervals or a few times in an entire lifetime Occasionally, however, they recur with some frequency varying from several times a year to several times a week Except in rare instances in which they recur frequently or are very prolonged they neither interfere with gainful work lead to heart failure nor shorten life In some persons attacks of atrial tachycardia foreshadow the development of atrial flutter or fibrillation In cases in which there is associated anatomic heart disease especially in cases of atrial tachycardia with atrioventricular block,[114] prolonged and severe attacks may lead to congestive heart failure,[90] and rarely to peripheral thromboses and gangrene Adams-Stokes syndrome and cardiac infarction without acute coronary occlusion Heart failure may be induced occasionally also in the apparently normal heart

Treatment of Atrial Tachycardia

Treatment is directed at (1) control of the acute attack of atrial tachycardia and (2) prevention of future attacks or diminution of their frequency in persons subject to frequent paroxysms

The Acute Attack The acute attack may sometimes be terminated by the patient if he is instructed to try to sit, leaning forward with his head down to lie prone across the bed with his head lower than his trunk, to take a deep breath with glottis closed after a complete expiration (Muller procedure), or to expire forcibly with glottis closed after a deep inspiration (Valsalva experiment) Sometimes a patient or a member of his family learns to abort the attack by firm (painful) pressure on one eyeball with the eyelid closed (oculocardiac reflex) Induced gagging and vomiting by irritating the pharynx with the finger is occasionally effective Most of the effective therapeutic measures restore sinus rhythm by vagal stimulation,[48] which diminishes the rate of impulse production in the sinoatrial and atrioventricular nodes

Carotid Sinus Stimulation The physician s most useful procedure is to massage the right carotid sinus and if this is ineffective the left carotid sinus for 10 to 30 seconds The carotid sinus may be located by feeling the strong carotid arterial pulsations at the bifurcation of the common carotid at the level of the upper border of the thyroid cartilage The patient should be recumbent with head extended and turned slightly to one side a pillow under the back of the neck Pressure and massage are best performed with two or three fingers compressing the artery and sinus posteriorly and medially against the vertebral spine A massaging motion is preferable to direct pressure lest the artery be compressed below the sinus itself I prefer to listen with my stethoscope or ear against the patient s precordium as I perform the massage In this way unnecessary prolongation of the procedure is avoided with the possible risk of syncope or cardiac standstill Cardiac auscultation is also important because carotid sinus pressure is often useful not only for terminating the attack but also for the differential diagnosis of the various forms of tachycardia (p 378) Attention is directed

to the occasional occurrence of transient or permanent monoplegia[73] or hemiplegia following carotid sinus stimulation.[24]

A similar vagal reflex may be induced by firm pressure over one eyeball at a time and then, if necessary, over both eyeballs simultaneously.

If these mechanical measures fail, a number of drugs may be employed, chiefly for their stimulating effect on the vagus nerve. *Reassurance* and the administration of a *sedative* (e.g., 0.2 gm. pentobarbital sodium) orally or by injection are important preliminary measures to the use of the more specific drugs.

Digitalis administered intravenously [illegible] now widely employed as the drug of choice in the treatment of atrial tachycardia. Cedilanid (lanatoside C) is utilized because of its rapid action and elimination and its lesser hazard than the somewhat swifter acting ouabain.[64, 1] As a rule, the ectopic tachycardia is converted to sinus rhythm without serious toxic symptoms with doses of 4 to [illegible] cc. (0.8 to 1.6 mg.). Weisberger and Feil[98] administered lanatoside C intravenously in a dose of 0.8 mg., repeated in 30 to 60 minutes if necessary. In 16 of 17 instances of paroxysmal tachycardia, the tachycardia stopped suddenly within 40 minutes after the first dose; in the remaining case it stopped within 12 hours. In 26 cases treated by Barrow[1] conversion was effected in all cases within a period of 1½ hours and often within 15 to 30 seconds. The usual dose was 1.2 to 1.6 mg. injected intravenously in 60 to 120 seconds. Digitalization may also be effected rapidly with the oral preparation of digitoxin. In general, full doses of digitalis should be given before discontinuing it as ineffective. (For preparations and methods of administration of digitalis, see p. 259.)

Ouabain (p. 262) is administered if there is great urgency. Acetylstrophanthidin was reported to restore sinus rhythm in 11 of 12 cases of supraventricular tachycardia.[6] But this drug may produce fatal arrhythmias[24, 63] and its use in the treatment of paroxysmal atrial tachycardia is rarely justified, particularly because of the availability of other effective drugs.

Phenylephrine (Neo-synephrine) hydrochloride[9, [illegible]] has taken the place of Mecholyl in my practice because of its equal effectiveness without the unpleasant and often alarming side actions of Mecholyl. I use Neo-synephrine whenever carotid sinus stimulation has failed to restore normal rhythm in paroxysmal atrial tachycardia. Thus far Neo-synephrine has been uniformly successful in my hands, often after many other measures have been tried and the attack has lasted for hours. The drug is believed to act by raising the blood pressure and thereby stimulating carotid sinus and aortic receptors with consequent reflex vagal stimulation.

Neo-synephrine hydrochloride, 1 per cent solution for intravenous use, is employed. I draw up 0.3 cc. in a tuberculin syringe, dilute with sterile saline or distilled water to 1 cc. and inject 0.3 cc. (0.9 mg.) of this rapidly intravenously, holding the needle in the vein. As a rule, sinus rhythm is restored within 60 to 90 seconds or less. If not, I slowly introduce the remainder of the solution intravenously. The drug is either contraindicated or should be given with great caution in patients with organic heart disease, severe hypertension, hyperthyroidism, partial heart block or marked bradycardia. Intense headache and anxiety may occur. Short runs of ventricular tachycardia have been observed following the use of Neo-synephrine in a patient with coronary heart disease and paroxysmal atrial tachycardia.[63] When there is any possible contraindication to Neo-synephrine, I prefer to administer a sedative and utilize Cedilanid intravenously if carotid sinus stimulation has failed.

Methoxamine (*Vasoxyl*) has been found equally effective[100, 18, 40] and possibly other pressor amines may be similarly employed to control paroxysmal atrial tachycardia. Methoxamine is administered intramuscularly or intravenously in a dose of 10 to 20 mg. Its action is similar to that of Neo-synephrine but is said to have the advantage of causing no increase in cardiac irritability. Nausea, weakness, apprehension, agitation and momentary asystole occur very briefly during the transition to sinus rhythm and may be quite upsetting to the patient.

Levarterenol (*Levophed*), 8 to 16 mg. in 1000 cc. of 5 per cent glucose, administered intravenously at the rate of 20 to 40 drops per minute and adjusted to raise the systolic blood pressure rapidly to 120 to 160 mm. Hg, was effective in terminating supraventricular tachycardia in 6 patients.[44]

Mecholyl (acetyl beta methylcholine chlor

ide), 20 mg (⅙ grain) administered hypodermically,[192] is being used less and less often (Fig 71) Unpleasant and sometimes alarming reactions occur, including extreme flushing of the face, perspiration, intense salivation a sense of choking or of imminent death and, rarely, collapse Nausea and vomiting are not uncommon, but usually at or after termination of the attack

Neostigmine injected subcutaneously in doses of 0 5 to 2 mg (1 to 4 cc of a 1 2000 solution) has also been employed in the treatment of supraventricular tachycardia,[203] but alarming reactions have been reported [8]

Pronestyl may also succeed in terminating attacks of atrial tachycardia [9] although it is generally less effective than in the control of ventricular tachycardia Nevertheless Berry and associates [8] established sinus rhythm with procaine amide in 18 of 22 episodes of supraventricular tachycardia, and Pascale et al [154] converted 10 of 13 episodes of paroxysmal supraventricular tachycardia to sinus rhythm It is particularly effective in nodal tachycardia [171] An intramuscular injection of 500 mg may be given and repeated in 2 hours if necessary [15] Or Pronestyl may be given intravenously no faster than 100 mg per minute, up to 1000 mg if necessary (p 375)

Potassium salts (p 267) have been employed to control the atrial tachycardia resulting from digitalis intoxication [65] If these are ineffective procaine amide is administered (p 340)

Magnesium sulfate, 15 to 25 cc of a 20 per cent solution injected intravenously, 5 cc at a time, has been effective in the control of paroxysmal tachycardia [226 64 100]

Other recommended measures with which I have had few experiences or little or no success include the oral administration of syrup of ipecac, 8 to 16 cc (2 to 4 drams), repeated if necessary until vagal stimulation is sufficient to induce vomiting, or the hypodermic administration of apomorphine (5 to 10 mg or 1/12 to 1/6 grain) Both of these procedures are drastic and rarely necessary In a few cases atabrine has controlled attacks of paroxysmal tachycardia [57] An intravenous injection of 0 4 gm of atabrine has restored sinus rhythm in a case of nodal tachycardia within 45 seconds [50]

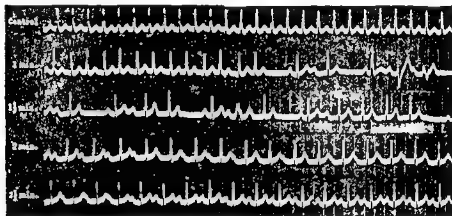


Fig 71 Paroxysmal atrial tachycardia Effect of 25 mg of Mecholyl Occasional slowing with sinus beats after one minute In lowest strip sinus rhythm with sinus tachycardia rate 130 per minute In next half minute normal rhythm with rate of 90

Quinidine is sometimes effective when all other measures have failed (For dosage, administration and toxicity, see p 368)

For prolonged attacks which do not respond to other measures, sedatives are usually necessary Bromides phenobarbital or chloral are most generally employed Occasionally morphine is justifiable and effective especially in the presence of distressing dyspnea shock or pain, but it is rarely needed and is contraindicated when attacks recur at relatively brief intervals The application of an ice bag to the precordium often affords psychologic and perhaps more specific benefit Reassurance is important

Treatment of Paroxysmal Tachycardia in Infants. This form of tachycardia is often associated with very rapid ventricular rate and heart failure and is notably (but not in

variably) resistant to carotid sinus massage and anti arrhythmic drugs But digitalization is usually effective Cedilanid is given intra muscularly or intravenously in an initial dose of 0 5 to 2 0 cc (0 1 to 0 4 mg or 0 01 mg per pound) Subsequent dosage is determined by the clinical response The simultaneous ad ministration of a sedative is desirable Oxygen therapy may also be valuable When there is no urgency digitalization may be effected by oral digoxin in a dose of 0 03 mg per pound in three divided doses in a period of 16 to 24 hours Digitalization is maintained for a week with one-tenth the digitalizing dose daily If the arrhythmia persists after full digitaliza tion, quinidine should be administered 100 mg orally every three hours for five doses or until the tachycardia stops Digitalization is main tained during quinidine therapy Phenyl ephrine 0 1 to 0 5 mg intravenously has been used successfully Morphine and anti biotics are important additional measures in the presence of congestive heart failure and pulmonary congestion or pneumonia

Prevention of Attacks The prevention of frequent attacks of paroxysmal tachycardia is difficult because of ignorance as to the under lying or precipitating cause All of the meas ures advised in the treatment of frequent extrasystoles should be employed (p 339) including the avoidance of emotional tension fatigue, tobacco coffee and alcohol indiges tion and constipation, unusual effort or exertion

Among drugs mild sedatives may be use ful but *quinidine* and *digitalis* are most de pendable The dosage of quinidine may start at 0 3 gm (5 grains) every two hours for six doses and may be increased gradually up to 4 gm (60 grains) daily in divided doses if necessary When the controlling dose is found it may have to be continued for months or years if the attacks recur when the drug is omitted Quinidine thus administered may eliminate recurrences entirely or diminish their frequency If quinidine is ineffective digitalization with continued maintenance doses of digitalis may prevent future attacks Digitalis is especially desirable in elderly pa tients with frequently recurring attacks

ATRIAL FLUTTER

This is a form of rapid heart action in which the atria beat regularly at a rate of 250 to 350 per minute The term flutter was first em ployed by MacWilliam[127] to describe the response of the atria to faradic stimulation Clinical features of atrial flutter were first described in detail by Jolly and Ritchie in 1910[99] Usually there is a 2 1 or some other fixed a v block, and the ventricles beat reg ularly at rates of 125 to 160 per minute Ventricular rates as high as 300 per minute may occur usually in infants in whom all the atrial impulses produce ventricular contrac tions An irregularity of the ventricular rate may result from changing a v conduction and altered degrees of a v block

Atrial flutter is encountered much less commonly than either atrial fibrillation or atrial tachycardia to both of which it is re lated in mechanism Conversion from atrial flutter to fibrillation occurs commonly, es pecially after the administration of digitalis Within the same electrocardiogram one may observe portions in which it is difficult to dis tinguish between atrial flutter and fibrillation or occasional shifts from atrial flutter to fibrillation and vice versa This is termed im pure flutter or flutter fibrillation

Atrial flutter usually occurs in paroxysms which persist much longer than those of atrial tachycardia, lasting many days weeks or months When flutter lasts more than two to three weeks, it is termed established flutter This type may persist indefinitely unless controlled by therapeutic measures Cases of *chronic atrial flutter* have been described[89, 108]

Mechanism

The mechanism of atrial flutter has usually been explained by either the theory of (a) "circus movement" or (b) repetitive stimuli from an ectopic focus in the atrium The theory of circus movement or circus rhythm was promulgated by Thomas Lewis[121] and his school and was widely invoked in the English speaking countries whereas the theory of repetitive stimuli from an ectopic focus was promulgated by Rothberger[146] and the Vien nese school Until recently, any controversy between these theories was usually confined to the quiet composure of the physiology classroom Since about 1949 the development of newer experimental techniques and numer ous experimental and clinical observations have revived the conflict between these theories without as yet a clear decision as to which applies to clinical atrial flutter

Circus Rhythms Circus rhythms or circus

movements were first induced in the umbrella of the jelly fish by Mayer,[135] who blocked a local area and applied a stimulus on one side of the block. The excitation wave thus initiated traversed the ring of the umbrella in a unidirectional fashion away from the block. If on completing the circuit and reaching the previous site of the block near its origin, the impulse (or wave) found the block gone and the tissue therefore no longer refractory, it continued to circle the ring a second, third, fourth time, etc. If no block had been set up at the original moment of stimulation, an excitation wave was able to spread along the ring in both directions (clockwise and counterclockwise) from its origin until both forward portions met and neutralized each other halfway along the circumference.

Further researches by Mines,[illegible] by Garrey[146] and by Lewis and his associates[131] disclosed that circus rhythms depended on (1) extreme shortening of the refractory period of the heart muscle, (2) slowing of the rate of conduction of an excitation wave, (3) local areas of block (or depressed excitability) and (4) rings of sufficiently large circumference.

Support for the theory of circus movement was recently found in the experimental studies of Rosenblueth and Garcia Ramos[165] (infra) and in curves of the momentary atrial electrical axes.[45] In cases of atrial flutter and fibrillation the curves of these axes were roughly circular, while the curve in cases of paroxysmal tachycardia resembled that of sinus rhythm.

According to Lewis et al., atrial flutter is due to an ectopic atrial impulse which traverses a circular path around the orifices of the superior and inferior venae cavae at an absolutely regular rate of about 250 to 350 per minute.[131] On returning to the ectopic center the impulse finds its site of origin no longer refractory. The original impulse thus reenters the circuit and continues around the same ring of muscle. According to this theory, the atrial rate is determined by the speed with which the impulse traverses the circuit and this, *in turn, by the conductivity, refractory* period and length of the circus ring of muscle. From the "circus" excitation wave, sometimes called the central or mother wave, centrifugal waves are said to flow uniformly and regularly to the various parts of the atrial musculature. This results in weak but distinct atrial contractions.

Theory of Repetitive Stimuli from an Ectopic Focus. Rothberger[166] and his school adhered to the theory that stimuli arising in ectopic or "parasystolic" foci were responsible for premature (ectopic) beats and also that repetitive stimuli from such foci produced paroxysmal atrial tachycardia, atrial flutter or atrial fibrillation, depending on the rate of impulse formation.

This concept was supported by recent studies of Scherf,[177] who devised a method for producing atrial arrhythmias including atrial flutter for prolonged periods, by the application of aconitine to a local area of the dog's atrium. Previously such atrial arrhythmias could be induced for only very brief periods during or shortly after electrical stimulation of a local atrial site. Scherf and associates found that cooling the aconitine site after the production of atrial flutter caused the flutter to disappear; the flutter reappeared when cooling was discontinued. These findings appeared incompatible with the concept of self-perpetuating circus movement. They concluded that atrial flutter was due to a continuous discharge from an ectopic focus, whereas atrial tachycardia results from rapid, interrupted discharges from such a focus.[176,177]

Prinzmetal and associates[157,118] in a series of beautifully conceived and executed studies, utilizing the aconitine technique for inducing atrial arrhythmias, found considerable evidence that both atrial flutter and fibrillation occur when an ectopic atrial focus discharges impulses at rapid rates. Observations by high speed cinematography indicated that the flutter wave travelled away from the aconitine focus in all directions and did not return toward the focus or form a circulating wave. Furthermore, direct leads were recorded from various sites throughout the interatrial septum and both atria, including the body of the left atrium which had not been previously explored in this manner. By timing the intrinsic deflections and studying the configuration of the recorded electrocardiograms, they concluded that the flutter wave started at the *ectopic focus and radiated simultaneously in* all possible directions.

Spontaneous atrial flutter in man was also studied by high speed cinematography of the atria observed at a cardiac operation[158] and by simultaneous multiple esophageal, precordial and limb lead electrocardiography. The films showed simultaneous contraction of the right

and left atrial appendices whereas one or the other would have preceded if appendiceal contraction resulted from a stimulus pursuing a circus movement The simultaneous esophageal electrocardiograms taken from different atrial levels indicated that the impulse responsible for atrial flutter usually arises in and travels away from the caudal region of the atrium (negative electrocardiographic deflection) whereas in the cephalic region of the atrium there was a positive deflection denoting passage of the impulse toward the cephalic region In the midatrial region there was a positive-negative diphasic complex indicating passage of the impulse toward the electrode at that site followed by passage away from the site toward the cephalic region If the circus theory applied one would expect identical deflections in esophageal leads from all atrial sites

On the other hand studies of esophageal and precordial leads in patients with atrial flutter by Cabrera Cosio and Sodi Pallares[97] and of endocardial and esophageal electrocardiograms and vectorcardiograms in such patients by Grishman et al [8] and of endocardial and esophageal electrocardiograms by Wenger and Hofmann Credner[207] were all interpreted as supporting the concept of circus movement The problem in evaluating these conflicting reports based on esophageal and precordial electrocardiograms is due at least in part to inability to follow the entire path pursued by the atrial excitation wave and the frequent difficulty in timing the intrinsic deflections accurately

It is highly probable at least in the experimental animal that the mechanism of atrial flutter is not a unitary one and that both repetitive stimuli from a single or multiple foci and circus rhythms may be responsible under different circumstances Aconitine induced atrial flutter may be due to the first mechanism On the other hand Rosenblueth and Garcia Ramos[183] established prolonged flutter by first crushing the intercaval bridge thus producing an area of block between the mouths of the venae cavae and then applying electrical stimulation to the right atrium The atrial flutter thus produced is generally accepted as being the consequence of a stimulus traveling in a circus movement The response of atrial flutter to various agents differs according to its production by aconitine or rapid electrical stimulation[33 131] additional evidence that experimental atrial flutter may be due to different mechanisms

In conclusion there is as yet no general agreement as to whether atrial flutter which may have a varied mechanism in the experimental animal is due to a circus movement or rapid stimuli from an ectopic focus in man Various modifications of both theories have been suggested to explain the controversial data[200]

Relation of Atrial Flutter to Paroxysmal Tachycardia and Other Atrial Arrhythmias A close relationship between the various atrial arrhythmias has long been indicated by the clinical observation of a gradual or rapid transition from isolated ectopic beats to paroxysmal (atrial) tachycardia atrial flutter and atrial fibrillation in the same patient The administration of drugs such as quinidine may result in rapid transitions from one to the other atrial arrhythmia As a rule atrial premature beats and atrial tachycardia appear in the same patient as do atrial flutter and fibrillation but rarely atrial tachycardia and atrial flutter In the experimental animal all four of the above-mentioned atrial arrhythmias could be produced depending on the rate of electrical stimulation Accordingly it has been suggested that these atrial arrhythmias have an identical origin e g rapid stimuli from an ectopic focus but that the specific resulting arrhythmia depends on the rate of stimuli formation Extrasystoles appear if the rate of discharge from the ectopic focus is less than that from the sinus node and tachycardia flutter fibrillation at progressively faster rates from about 180 to 600 per minute

Nevertheless in their clinical behavior paroxysmal atrial tachycardia and atrial flutter differ sufficiently to indicate that these arrhythmias may be caused by different mechanisms Atrial tachycardia usually occurs in normal hearts flutter in diseased hearts Atrial tachycardia responds readily as a rule to carotid sinus pressure (vagal effect) Mecholyl and sympathomimetic amines with restoration of sinus rhythm whereas atrial flutter does not so respond Digitalis often converts atrial flutter to fibrillation whereas atrial tachycardia is restored to sinus rhythm without the intermediary of atrial fibrillation

Atrial tachycardia and flutter are not absolutely distinguished by the atrial rate since

occasionally atrial tachycardia is associated with atrial rates of about 300 per minute, whereas in atrial flutter the atrial rate is occasionally less than 225 per minute It has been suggested that the important difference is not the atrial rate as such but the inability of the atrioventricular bundle to conduct all of the e atrial stimuli in atrial flutter Hence atrioventricular block is common in atrial flutter, very rare in clinical atrial tachycardia, except that due to digitalis intoxication or electrolyte disturbances[131 70] The classic electrocardiographic distinction between paroxysmal atrial tachycardia and atrial flutter is the presence of continuous oscillations without isoelectric intervals in atrial flutter (Fig 75) There is often a sharp upstroke with a more gradual downstroke forming a characteristic series of continuous oscillations resembling saw teeth (F waves) without distinct isoelectric intervals However, Prinzmetal and associates[1 7] discovered isoelectric intervals corresponding to atrial diastole in 95 per cent of 139 cases of spontaneous atrial flutter The undulatory pattern of the flutter waves was said to be composed of two components a P wave of depolarization followed by a Ta wave of repolarization The P waves are best seen in leads II and III of the standard leads and are indistinct in lead I because the presumed pathway of the ectopic impulse is perpendicular to the direc

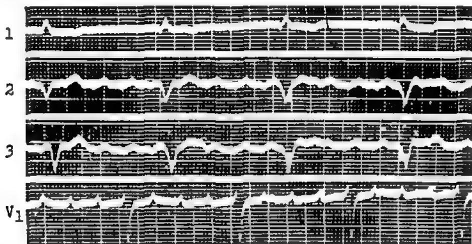


Fig 72 Atrial flutter in a man aged 61 year with anteroseptal and diaphragmatic infarction 4 1 ventricular response observed in lead V_1 Ventricular rate 50 atrial rate 200 per minute

tion of lead I whereas its course is more nearly parallel to the direction of leads II and III In most cases of flutter, the P wave is inverted in leads II and III suggesting that the excitation wave arises in the caudal portion of the atrium less frequently there is an upright P wave in leads I and II indicating that the ectopic focus is in the cephalic portion of the atrium Most of the precordial leads do not usually disclose the P waves distinctly, however the P waves are usually well displayed in leads from the right side of the sternum (V_1 V_{3R}), e g, by placing the exploring precordial electrode in the third right interspace[5] The latter or esophageal leads should always be obtained in the study of any paroxysmal tachycardia especially in cases in which a rapid ventricular rate obscures the P waves They are particularly helpful in dis-

But this has been challenged by Prinzmetal et al[157 158]

Conduction of all the very rapid atrial impulses to the ventricle is rarely possible Occasionally in infants and rarely in adults[157] there is a 1 1 ventricular atrial rate the ventricles contracting regularly 250 to 300 times a minute But as a rule there are varying degrees of partial heart block (2 1, 3 2 3 1, etc) Most commonly the ventricular rates vary between 100 and 150 per minute and there is a 2 1 block With higher degrees of block, e g, 4 1, the ventricles may beat regularly and at normal rates (Figs 72 75) Complete heart block with atrial flutter has also been noted[11 115]

The Electrocardiogram

The *P waves* are absolutely regular in rhythm at rates of 250 to 350 per minute

closing atrial flutter with 2 1 block Often the typical flutter waves are seen distinctly in aV$_F$

The *P R interval* is prolonged but it is often difficult to measure It may vary from beat to beat especially in cases with varying grades of a v block [79] Even with unaltered grades of heart block e g 2 1 slight alterations in the R R interval may result from corresponding changes in the P R interval

The *QRS complexes* usually recur regularly at rates of 75 to 150 per minute except as noted above with changing P R intervals or degree of a v block Rarely there is a 1 1 block with ventricular rates of 250 to 300 or more In cases of atrial flutter with 1 1 response or even with 2 1 response the P waves may be obscured and the sequence of QRS complexes resembles a ventricular tachycardia (Fig 73) Atrial flutter with bundle branch block may also simulate ventricular tachycardia (Fig 74) Most commonly a QRS complex follows every second P wave occasionally every third or fourth P wave In such instances every second third or fourth P wave may be fused with or obscured by the QRS complex In long electrocardiographic strips there may be seen changing grades of block but usually there is a dominant degree of heart block Similarly the P R interval may vary in length but there is a tendency to return to a dominant time interval [79] The Wenckebach phenomenon may occur in association with atrial flutter and varying block [28] Atrial flutter may be associated also with complete heart block and usually presents itself as chronic atrial flutter [23]

If an electrocardiogram is taken during carotid sinus pressure the atria are found to be unaffected while the ventricular rate is slowed and the degree of a v block may be increased Occasionally momentary cardiac standstill may occur These effects result from vagal stimulation which impairs conduction through the a v node Digitalis usually produces similar effects The intravenous administration of procaine amide may aid in differentiating atrial flutter with bundle branch block from paroxysmal ventricular tachycardia [III] In ventricular tachycardia the QRS complexes remain regular or become regular and their conformation changes

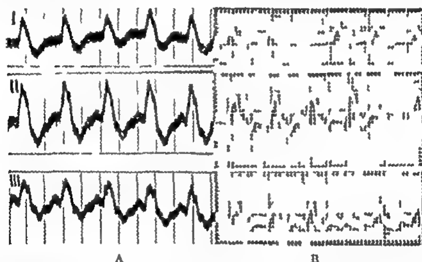


Fig 73 A Atrial flutter with 2 1 response resembling ventricular tachycardia Presence of flutter confirmed by jugular venous tracing
B Same case After digitalization flutter waves clearly seen especially in lead III

Etiology

Atrial flutter, like fibrillation and unlike atrial tachycardia is observed more commonly with heart disease than in its absence Its greatest frequency is with rheumatic heart disease and mitral stenosis but it may also be associated with hyperthyroidism (p 1006) or with coronary and hypertensive heart disease [102] It occurred in 20 of 1247 cases of myocardial infarction [19] The tachycardias of infancy occurring usually in the first month of life are generally unaccompanied by an

underlying cardiac affection but may be due occasionally to rhabdomyoma of the conduction system or other myocardial disease Cases of *congenital* paroxysmal tachycardia[3] have been distinguished from those commencing in the early months of infancy by their equal occurrence in males and females and by the predominance of atrial flutter in the congenital cases Atrial flutter may be observed with mediastinal disease and during surgical procedures especially those in the thoracic cavity[83] Occasionally it appears in patients without apparent heart disease either spontaneously or because of alleged nervous or physical strain or respiratory infection Atrial flutter occurs commonly during the administration of quinidine to patients with atrial fibrillation[199] it is rare manifestation of digitalis toxicity[44]

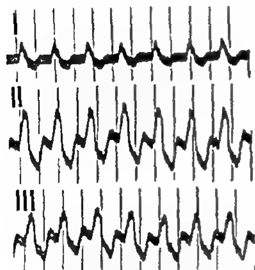


Fig 74 Atrial flutter with bundle branch block simulating ventricular tachycardia.

Symptoms and Signs

The symptoms are those of any sudden paroxysmal tachycardia namely palpitation anxiety ranging to alarm of impending death weakness dizziness or syncope and possible symptoms and signs of congestive heart failure or shock, as detailed under paroxysmal atrial tachycardia (p 346)

The paroxysmal tachycardia of early infancy may be due to atrial flutter While the tachycardia may be discovered accidentally it is usually documented by the infant's refusal to take food, vomiting, restlessness pallor, and later cyanosis striking rapid enlargement of the liver, dyspnea with noisy respiration, pulmonary edema and other evidences of congestive heart failure[137] [illegible] (p 347)

The heart rate in atrial flutter is rapid and usually regular despite rest, exercise or change of posture Auscultation of the heart discloses apical rates of 125 to 160 when there is 2 1 block but the rate may be 75 or 100 with blocks of 4 1 or 3 1 respectively Sometimes there is a sudden change in rate from 160 to 80 as the degree of block alters from 2 1 to 4 1 Carotid sinus stimulation usually increases the degree of block When the ventricular response and therefore the cardiac beats are irregular exercise may raise the ventricular rate and induce a constant degree of block and a regular heart beat A changing intensity in the first heart sound in cases with irregular ventricular response may be due to the alterations in the P R interval [illegible] The atrial contractions in atrial flutter with high grade heart block may be heard as distinct clicks[149] [illegible]

Inspection of the cervical veins may disclose distinct "a" waves of atrial contraction which are two three four or more times as frequent as the apical (ventricular) waves When present these "flutter" waves are diagnostic

There may also be physical signs of an underlying cardiac disease or of associated circulatory failure The circulatory dynamics are determined essentially by any intrinsic cardiac disease Conversion of the flutter to sinus rhythm may[4] or may not[137] induce an increase in the resting cardiac output

Prognosis

The attack of flutter is apt to be more disturbing than that of atrial tachycardia because of its greater tendency to persist (days weeks months or years)[44] Cases of atrial flutter lasting eleven years[10] twenty four years[133] and twenty six years[10] have been reported Sometimes it is very difficult to alter the atrial flutter or to reduce to ventricular rate satisfactorily despite full doses of digitalis or quinidine Because of the prolonged duration and the frequency of underlying heart disease atrial flutter is apt to be complicated by the development of congestive heart failure However it is remarkable how patients with normal heart despite atrial flutter, or with ventricular tachycardia of months or years' duration suffer no visible deterioration of their cardiac function Sometimes the

attacks are disabling by their very persistence even when circulatory function remains adequate Embolization occurs occasionally Relapses of flutter occur frequently after sinus rhythm has been restored Often atrial flutter is followed sooner or later by atrial fibrillation This may occur spontaneously or in response to digitalis therapy

Treatment

Treatment consists essentially in the administration of digitalis or quinidine *Digitalis* is usually given first trial and is employed to slow the ventricular rate and to control or prevent heart failure The digitalis should be given in full doses i e until the desired therapeutic effect is obtained Often speedy digitalization is desirable and is effected by the intravenous administration of lanatoside C (8 cc or 1 6 mg) (p 263) Distinct signs of toxicity may appear with effective dosage (For doses and methods of digitalization see p 259) The ventricular rate is usually reduced to the normal range by an increase in the degree of av block or the flutter may be converted to atrial fibrillation and the ventricular rate is slowed to desired levels (Fig 75) In either circumstance daily maintenance doses of digitalis (p 261) may be continued as required to maintain the desired apical rate Digitalization may be followed by prompt restoration of sinus rhythm without the intermediation of atrial fibrillation Sometimes in cases with induced atrial fibrillation discontinuation of the digitalis is followed by a reversion from atrial fibrillation to normal sinus rhythm If not the necessary doses of digitalis should be resumed or an effort be made to restore normal sinus rhythm with quinidine

Quinidine may be administered as described below under atrial fibrillation whenever atrial flutter or atrial fibrillation persists after digitalis therapy When atrial flutter is treated with quinidine there may be a progressive reduction in the degree of block from 4 1 to 2 1 and 1 1 the latter being associated with an extremely rapid ventricular rate and sometimes with disabling and alarming clinical manifestations [133] As a rule this is transient and the previous block is restored with discontinuation of quinidine Carotid sinus massage may terminate an attack of atrial flutter with 1 1 conduction In cases of frequent relapsing atrial flutter quinidine may also be given after an attack is controlled in the hope of preventing or minimizing recurrences

Although *procaine amide* (Pronestyl) is usually most effective in ventricular arrhythmias it may also be effective in atrial arrhythmias Restoration of sinus rhythm has been reported in atrial flutter with 1 1 block following 6 cc (0 6 gm) of Pronestyl intravenously [55] However as a rule Pronestyl is ineffective in terminating atrial flutter [2] although the atrial rate may be slowed [184]

Reassurance avoidance of emotional and physical stresses when possible and elimination of tobacco coffee and alcohol indigestion constipation and other factors which may seem to contribute to the attacks should all be considered as accessory therapeutic measures



Fig 75 Atrial flutter Effect of digitalis Feb 25 atrial flutter with 2 1 response Atrial rate 340 Ventricular rate 170 Feb 27 4 1 response Ventricular rate 85 Patient digitalized Four days later atrial fibrillation Digitalis discontinued Mar 4 return of regular sinus rhythm

ATRIAL FIBRILLATION

This is an arrhythmia characterized by extremely rapid irregular atrial impulses by ineffectual vermicular atrial contractions and by irregular rapid ventricular beats Cushny and Edmunds[49] first interpreted atrial fibrillation in man as synonymous with the perpetually irregular pulse of Hering[101] and the physiologist s delirium cordis Rothberger and Winterberg[167] and independently Lewis[126] proved this electrocardiographically

Atrial fibrillation is one of the two or three commonest and probably the most important of all the disorders of the heart beat It may occur as paroxysms of an irregular tachycardia or more often it becomes established as a permanent condition

Mechanism (See also p 1003)

The mechanism of atrial fibrillation like that of atrial flutter has been explained by

either the theory of circus movement or the theory of rapid discharges from one or more ectopic foci. This has been discussed in some detail above (p. 352). That atrial flutter and fibrillation are closely related is indicated by their frequent association in laboratory animals and humans and their frequent change from one to the other, especially as a result of drugs. Consequently, their mechanism is regarded as similar. Lewis[131] concluded that both were due to a circus rhythm but that the actual rhythm was regular in flutter, irregular in atrial fibrillation. Recent support for the circus movement theory for atrial fibrillation as for atrial flutter (p. 352) was contributed by the observations of Rosenblueth and Garcia Ramos,[165] who produced atrial fibrillation by electrical stimulation after blocking or crushing the intercaval bridge of tissue.

Rothberger[166] believed that atrial fibrillation arose as a result of rapid discharges from an ectopic focus. Scherf concluded that atrial fibrillation produced with aconitine was due to a continuous discharge from a single ectopic focus, whereas that produced with acetylcholine was of multifocal origin.[177]

Prinzmetal et al. made direct observations on the fibrillating atria of patients undergoing cardiac surgery with the aid of high speed cinematographs and direct atrial leads.[159] Heterorhythmic large (L) contraction waves at an irregular rate of 250 to 400 per minute were noted and corresponding irregular atrial electrocardiographic complexes at the same rate, presumed to correspond to the f waves seen in the standard leads of the electrocardiogram during atrial fibrillation. The configuration of these irregular varying complexes and their occurrence at different rates in the two atria were regarded as findings which were incompatible with the circus movement theory and supporting that of rapid stimuli from ectopic foci. Similar studies of atrial fibrillation produced experimentally in animals by aconitine or electrical stimulation disclosed chaotic, bizarre and heterorhythmic atrial motion. Large grossly visible L contractions were observed at the rate of 400 to 600 per minute and minute asynchronous contractions and dilatations (*M activity*), *best seen under high magnification*. Corresponding electrical activity was recorded. These observations were also interpreted as incompatible with the circus movement theory. Prinzmetal et al.[159] have stressed the failure of the atrial myocardium to conduct these extremely rapid impulses as a prerequisite to the development of atrial fibrillation. Atrial fibrillation either follows atrial flutter or is initiated by an extrasystole occurring during the vulnerable period of the cardiac cycle. Myocardial disease or dysfunction and aging predispose. It is presumed that the atria are unable to respond in a coordinated manner both because of the excessively *rapid impulses arising from an* ectopic focus and because of a deficiency in the atrial musculature.

Atrial Behavior in Atrial Fibrillation. There is no definite coordinated universal atrial contraction or diastolic relaxation. Instead there are irregular, dissociated contractions at *about 400 per minute*, which produce wormlike (fibrillary) quiverings of the atria without an effective atrial contraction. So-called impure flutter or flutter-fibrillation represents an intermediary or transition phase between flutter and fibrillation, combining features of both disturbances.

Ventricular Behavior. Like atrial flutter, atrial fibrillation is associated with various degrees of a-v block. But because of the more rapid atrial rates in fibrillation, fewer impulses can reach or excite the ventricles and, because the atrial rhythm is irregular, the ventricular rhythm in atrial fibrillation is also irregular. Only about one out of three or one out of four atrial impulses gains access to the ventricles, and consequently the ventricular rate usually varies between 100 and 140 per minute. In patients without organic heart disease and in the paroxysmal type of atrial fibrillation, higher rates even approaching 180 to 200 may be observed.

Under certain circumstances atrial fibrillation is associated with ventricular contractions which are *irregular in rhythm* but *normal or slow in rate*.

1. In *partial heart block* due to underlying rheumatic myocarditis, calcific aortic stenosis or severe coronary artery disease, the ventricular rate may range between 90 and 40 per minute.

2. *Carotid sinus pressure*, by causing reflex vagal stimulation, depresses a-v conduction and slows the ventricular rate.

3. *Digitalis*, by direct action on the a-v node and bundle, diminishes atrioventricular conduction and in therapeutic doses may slow the ventricular rate to between 60 and 80 per

minute Thus, when patients with atrial fibrillation are adequately digitalized their heart beat if sufficiently slowed may appear to be regular The irregularity becomes clear if the rate is increased by exercise or amyl nitrite

Under other circumstances the *ventricular contractions* in cases of atrial fibrillation may actually become *regular* with slow or rapid rates as follows

1 *Complete heart block* in association with atrial fibrillation No atrial impulses are transmitted to the ventricles and the latter respond regularly and slowly to their own pacemaker (idioventricular rhythm) Exercise does not restore the irregularity

2 *Ventricular paroxysmal tachycardia* The ventricles respond rapidly and regularly to stimuli from an ectopic ventricular center and prevent excitation by stimuli from the fibrillating atria

capacity for physical exertion Furthermore the baneful effect of atrial fibrillation is indicated by the occurrence of heart failure in subjects with atrial fibrillation without apparent underlying heart disease In a series of 84 patients with atrial fibrillation who had no apparent organic heart disease there was evidence of frank or latent heart failure in fourteen [154] After conversion of the atrial fibrillation to sinus rhythm the increased cardiac size abnormal dynamics and heart failure were restored to normal

The Electrocardiogram

The characteristic electrocardiographic features of atrial fibrillation are (Fig 76)

1 *Absence of P waves* But there are usually continuous slight undulations known as f or fibrillation waves Sometimes these are visible only in precordial leads taken from the right side of the sternum or in esophageal leads [84]



Fig 76 Atrial fibrillation 8/21/40 regular sinus rhythm 8/7/43 atrial fibrillation Irregular rapid ventricular rate about 120 to 160 P waves absent 8/11/43 patient digitalized Atrial fibrillation persists but ventricular rate is slowed to about 75 per minute Coarse atrial fibrillary undulations but no distinct P waves

Effect on Cardiac Function The absence of effective atrial contraction removes a significant factor in the filling of the ventricles According to the observations of Lewis[1 8] and of Wiggers and Katz [13] this may amount to 20 to 30 per cent of the total ventricular contents Studies of cardiac output suggest that it is considerably reduced during atrial fibrillation for with the restoration of sinus rhythm the cardiac output increases 25 to 30 per cent [117 119 81] Increased cardiac output during exercise after conversion to sinus rhythm was reported by Kory and Meneely [118] Hecht et al [46] and others [33] The ability to increase cardiac output may be lost despite conversion to sinus rhythm if there is an underlying tight mitral stenosis or severe congestive heart failure From the clinical viewpoint it appears that fibrillation of the atria does not significantly impair cardiac function if the ventricular rate is sufficiently slowed to permit adequate diastolic filling However the advantage of sinus rhythm over atrial fibrillation may become apparent in an increased

2 *Irregularly spaced QRS complexes* They also vary somewhat in their configuration Occasionally notching slurring or widening of the QRS complex (intraventricular conduction disturbance) due to fatigue of the conduction tissues is observed in cases with ventricular rates of 180 or more

In cases of impure flutter there are occasional series of regular or almost regular P waves which vary in contour (sometimes termed F waves or P) However the R R intervals change from cycle to cycle In other portions of the same record the P waves disappear altogether and are replaced by f waves Flutter fibrillation is a term sometimes applied to these impure flutters which vary from moment to moment in their resemblance to flutter or fibrillation respectively (Fig 77)

Etiology

Atrial fibrillation occurs most commonly in cases of mitral stenosis (rheumatic heart disease) coronary heart disease with heart failure and hyperthyroidism [45 110] When es

tablished atrial fibrillation complicates hyperthyroidism there is often a simultaneous mitral stenosis or severe coronary disease (p 999) Paroxysmal atrial fibrillation is particularly identified with hyperthyroidism although it is also associated with a variety of other conditions Masked hyperthyroidism *may be overlooked as the cause of atrial* fibrillation Bortin and associates [illegible] utilizing radioactive iodine uptake for diagnosis discovered 8 instances of previously undetected hyperthyroidism among 35 cases of atrial fibrillation of uncertain etiology but attributed to coronary or rheumatic heart disease on insufficient grounds Atrial fibrillation *may occur in any type of heart disease es-*dition In particular, I have observed atrial fibrillation after surgical operation in the thorax[2] and also in the abdominal cavity, during pneumonia and less often with other infections with pulmonary and mediastinal carcinoma and mediastinal lymphomata after burns with biliary and renal colic and with visceral embolization and infarction, especially pulmonary embolization In some of these conditions I have strongly suspected the presence of underlying cardiac disease as a predisposing factor In others there is direct invasion of the heart muscle by neoplasm or inflammatory tissue

There are however also instances of purely *functional chronic atrial fibrillation without*

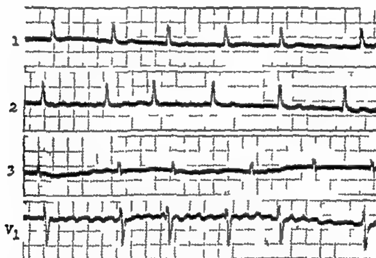


Fig 77 Atrial fibrillation with flutter fibrillation V_1 shows prominent fibrillation (f) waves resembling flutter (F) waves Ventricular rate 70 80 per minute and rhythm completely irregular Atrial rate in V_1 approximately 300 per minute and irregular

pecially in association with congestive heart failure It is also not infrequent in the first two weeks after an acute myocardial infarction when it appears as a paroxysmal occurrence which usually subsides spontaneously after several hours Askey[10] reported 84 instances of atrial fibrillation among 1247 cases of acute myocardial infarction Atrial fibrillation has been reported in cases of hemochromatosis in which hemosiderin pigment was demonstrated at autopsy in the atrial and ventricular myocardium [11,14]

Although atrial fibrillation is usually associated with severe organic heart disease it is occasionally discovered in patients with apparently normal hearts in whom the arrhythmia is precipitated by some noncardiac conanatomic disease of the heart occurring in 5 or 6 per cent of all cases of atrial fibrillation [1,6,47] In some tobacco alcohol or other toxic factors appear to be precipitating or contributory causes There are reports of cases of atrial fibrillation in acute nicotine poisoning[2] and following the prolonged use of thyroid extract [99] In others fatigue emotional stress or violent exertions have been indicted but there may be no apparent cause whatever Rarely atrial fibrillation may be induced by carotid sinus pressure [149] Familial occurrence has been reported[1,6,13], I have observed two brothers with atrial fibrillation without apparent organic heart disease who were said to have had this condition paroxysmally since youth and for at least twenty

years Since this was first written I have seen the 28 year old son of one of these brothers for recurrent paroxysmal atrial fibrillation without apparent heart disease

Paroxysmal atrial fibrillation may occur with any of the above conditions but it is especially associated with hyperthyroidism (p 1006) The atrial fibrillation observed after thoracic surgical procedures pneumonia etc lung disease, females predominate in hyperthyroidism and mitral stenosis males in coronary heart disease

Symptoms

Symptoms referable to atrial fibrillation vary considerably and are often obscured by the symptoms of the associated cardiac or noncardiac disease In paroxysms of atrial fibrillation or at the onset of permanent fibrillation the ventricular rate is usually very rapid and the symptoms are those already described under paroxysmal tachycardia (p 346) Most commonly there is palpitation but there may also be precordial oppression or pain anxiety or agitation and weakness or dizziness *The first or subsequent paroxysms may announce themselves by an* attack of syncope due to complete cardiac standstill of several seconds duration when

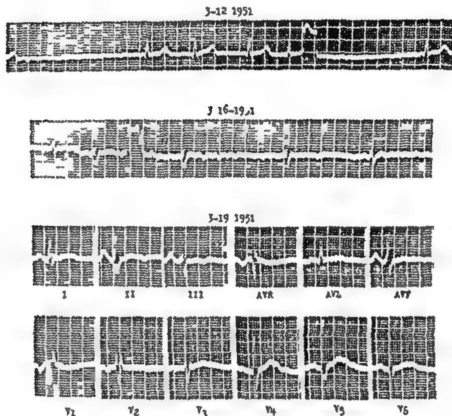


Fig 78 Man 35 years old with 10 year history of atrial fibrillation without evidence of organic disease Electrocardiogram during attack of syncope

3-12 51 Period of ventricular asystole in recumbency Extreme hypotension on arising

3-16-51 Atrial fibrillation with shorter periods of ventricular asystole after 0 8 mg atropine intravenously

3 19-51 Sinus rhythm established after 3 2 gm quinidine in 24 hours Prominent wide P waves in leads 2 3 aVR and aVF RR pattern in V to V and prominent U waves Intraatrial and intraventricular conduction defects and U waves due to quinidine

is usually paroxysmal in character and of brief duration

Atrial fibrillation occurs at any time between childhood and old age but most frequently after forty [140] As might be anticipated, the average age of patients with atrial fibrillation and coronary heart disease is about twenty years more than that of patients with rheumatic heart disease and this arrhythmia The ex incidence in cases of atrial

atrial fibrillation Symptoms of congestive failure or shock are apt to appear only if the tachycardia is very rapid (over 180) or if the attack is prolonged and the underlying cardiac disease has already greatly impaired myocardial reserve However congestive heart failure has been observed to result from uncontrolled atrial fibrillation in an otherwise normal heart [154] Syncope as well as dizziness occurs occasionally in chronic atrial fibrillation[154] as well as at the onset of a paroxysm [45] In one patient with atrial fibrillation for 10 years, with an apparently normal heart, the attacks of syncope ceased after sinus rhythm was restored by quinidine[73] (Fig 78)

Established atrial fibrillation is usually better tolerated than the paroxysmal type, partly because the rate is slower and partly because the patient becomes adjusted to the disturbance For these reasons the symptoms in established atrial fibrillation are usually those of heart failure and not of the arrhythmia Occasionally atrial fibrillation is discovered in patients who are completely unaware of any cardiac disorder In some atrial fibrillation is present on certain days and sinus rhythm at other times Nevertheless there may be no detectable difference in the patient's sense of well being Asymptomatic atrial fibrillation with slow ventricular rate may become distressing if the ventricular rate becomes accelerated by exercise emotional excitement febrile disease or drugs It is apparently the tachycardia rather than the ventricular irregularity that is chiefly and usually responsible for symptoms

Certain *complications* may be precipitated by a paroxysm or at the onset of permanent auricular fibrillation

1 *Heart failure* may be induced by the added burden of the irregular tachycardia on an already diseased heart The heart failure induced in some instances of atrial tachycardia is usually rapidly reversible with spontaneous or induced restoration of sinus rhythm But although the heart failure associated with atrial fibrillation may be controlled, it is usually chronic and requires continuous treatment thereafter

2 *Atrial thrombosis* is favored by the occurrence of atrial fibrillation For this reason atrial fibrillation is not infrequently a predisposing factor to cerebral, peripheral or visceral embolization and infarction Sometimes the emboli are dislodged when the atrial fibrillation reverts to normal rhythm spontaneously or after quinidine therapy Very occasionally in cases of mitral stenosis, the atrial thrombus formed after the onset of atrial fibrillation may continuously or intermittently obstruct the narrow mitral orifice (ball valve thrombus) causing a shock like picture and death (p 657) Of course atrial thrombosis may occur in mitral stenosis even with sinus rhythm if there is left atrial dilatation But it is probable that the absence of effective atrial contraction in atrial fibrillation is a major causative factor in thrombus formation Because of the danger of cerebral embolism, patients with atrial fibrillation are subject to sudden death According to Daley et al [illegible] 2 5 to 4 0 per cent of patients with atrial fibrillation die suddenly and unexpectedly

Signs

The distinctive physical sign is a complete irregularity of the heart beat This is most readily ascertained at heart rates of 100 to 140 Regularity may be simulated when the ventricular rate is under 90 or over 150 The pulse also is completely irregular At rapid ventricular rates however the pulse rate is usually considerably less than the apical rate, this difference is termed a pulse deficit It results chiefly from failure of the weak ventricular beats to open the semilunar valves and expel the column of blood which produces the radial pulse In part also the pulse deficit results from difficulty in counting weak pulse beats which are closely spaced Because of the possibility of a pulse deficit, it is essential that the heart rate be determined by cardiac auscultation, especially when this is being used as a guide to treatment

When treatment with digitalis has been instituted, the apical heart rate becomes slowed the beats become stronger and more uniform in amplitude, and the pulse deficit diminishes and then disappears If the patient is first seen at this stage of digitalization, the heart and pulse rate may be found within a normal range of 70 to 80 and the heart and pulse may appear to be regular or almost so

Heart Sounds The second sound may be absent when the ventricular contractions, which occur after a brief diastole and incomplete filling are too weak to open the semilunar valves The first sound varies in

loudness except when atrial fibrillation is associated with mitral stenosis [161]

Other physical signs are determined by associated cardiac or noncardiac disease Since mitral stenosis is the commonest underlying condition enlargement of the left atrium straightening or prominence of the left middle border of the heart and an apical diastolic murmur may be found The typical presystolic rumble is usually absent or difficult to elicit in the presence of atrial fibrillation If the heart rate is rapid the diastolic murmur is sufficiently close to the first sound to simulate a presystolic murmur When the heart rate is slow or the diastolic period is relatively long there is an early diastolic murmur

Diagnosis

For diagnosis and differential diagnosis of the tachycardias see page 378

Course and Prognosis

Paroxysms of atrial fibrillation usually last for several hours or occasionally for a few days When they persist for more than two weeks they usually are permanent unless specific treatment restores sinus rhythm Paroxysms may occur infrequently or several times a week Often a stage of paroxysmal atrial fibrillation precedes permanency of the arrhythmia The persistence and recurrence of paroxysmal atrial fibrillation are usually determined by some underlying cause such as hyperthyroidism or mediastinal disease The outlook then depends on the ability to discover and remedy the causative condition Atrial fibrillation developing from several days to two weeks after the onset of an acute myocardial infarction is almost always paroxysmal and of brief duration According to Brill [27] 90 per cent of paroxysms of atrial fibrillation subside within a week but occasionally one may continue for as long as a year and yet cease spontaneously On the other hand it is generally stated that once established atrial fibrillation tends to persist permanently Exceptions to this statement were reported by Burch [32] who observed atrial fibrillation of twenty two months duration replaced by sinus rhythm and by Fogel [73] who observed spontaneous return to normal sinus rhythm after a purported duration of eleven years

When paroxysmal atrial fibrillation occurs in a normal heart it may be quite disturbing because of symptoms due to the tachycardia because of the associated anxiety and rarely because of syncope or embolism But it is usually of no importance as regards the outlook for life or the development of heart disease [214] When paroxysmal atrial fibrillation occurs in a diseased heart the condition may be more serious because of the greater likelihood of precipitating congestive heart failure and the dangers of cerebral and peripheral ischemia embolism or sudden death

As a rule the development of persistent atrial fibrillation is an unfavorable prognostic sign In most instances it is associated with serious organic heart disease and its occurrence usually denotes advanced disease with congestive heart failure in the offing if not already present Persistent atrial fibrillation in patients with acute myocardial infarction is associated with a significantly higher mortality rate than in patients without this arrhythmia This may be a consequence of more extensive cardiac damage in the cases in which atrial fibrillation developed rather than of the arrhythmia itself Persistent atrial fibrillation in patients with hyperthyroidism is also a harbinger of early heart failure (p 999) However the outlook in this disease is less serious because with the elimination of hyperthyroidism both the atrial fibrillation and heart failure usually disappear rapidly

Aside from its unfavorable implications established atrial fibrillation may itself contribute to an unfavorable prognosis The effect of the rapid ventricular rate and the loss of effective atrial contraction in impairing cardiac function and inducing heart failure have been mentioned On the other hand atrial fibrillation in a patient with heart failure may sometimes denote a better outlook than sinus rhythm and heart failure [4] For if the atrial fibrillation is replaced by sinus rhythm after quinidine therapy or after thyroidectomy in cases of hyperthyroidism the heart failure may likewise disappear Or if this is not possible slowing of the rapid ventricular rate by digitalis and rest usually effects a striking improvement These observations are applications of the general theorem that the outlook in heart failure is better if a causative factor can be found and eliminated than when there is no apparent remediable cause

TREATMENT

Digitalis quinidine and occasionally *procaine amide* are the drugs usually employed

The treatment of atrial fibrillation depends somewhat on whether this arrhythmia is established or paroxysmal and in the latter type whether an effort is being made to eliminate or to prevent the attacks. When paroxysmal atrial fibrillation is associated with a very rapid ventricular rate emergency treatment is indicated. Digitalization by the intravenous or oral route is swiftly effected. The use of quinidine or Pronestyl is considered *after the ventricular rate is slowed*. When atrial fibrillation is due to overt or masked hyperthyroidism sinus rhythm may be restored by correction of the hyperthyroidism with radioiodine,[4] thiouracil[illegible] or by subtotal thyroidectomy. Treatment may be unnecessary if there are no symptoms due to the arrhythmia or if paroxysms subside spontaneously after a very brief duration and recur infrequently. In general digitalis is indicated if there is evidence of circulatory insufficiency and preferred if there is significant underlying cardiac disease even without heart failure. Quinidine is usually given first choice if the arrhythmia is a symptomatic disturbance, is of recent duration and if there are no apparent heart disease, no significant cardiac enlargement and no heart failure. Quinidine is often employed when atrial fibrillation persists for more than a week after thyroidectomy for hyperthyroidism (p. 1012) or if it develops during mitral commissurotomy and persists for more than a week postoperatively. Pronestyl is most apt to be effective in paroxysmal atrial fibrillation.[3]

Sometimes, despite the usual contraindication in cases with heart failure, quinidine may be *employed with lifesaving effect after digitalis* and other therapeutic measures have failed.[8] Similarly in patients with repeated embolization, with and without heart failure, quinidine has been given when the outlook was poor and has been effective not only in restoring sinus rhythm but also in terminating the embolization and improving the circulation.[211] When the ventricular rate is slow due *to partial or complete heart block quinidine* is contraindicated.

The restoration of sinus rhythm appears important both because of the greater risk of arterial embolism when there is atrial fibrillation and because of the improvement in circulatory dynamics with sinus rhythm, especially in the cardiac response to exercise (p. 359). In recent years I have advocated that at least one vigorous attempt be made to convert virtually all cases of chronic atrial fibrillation to sinus rhythm with the aid of quinidine. Occasionally, arterial embolism occurs within 24 to 48 hours after conversion to sinus rhythm. It has appeared to me that the embolism took place not during conversion to sinus rhythm, but with recurrence of the atrial fibrillation. I have been greatly impressed by the simple fact that *arterial embolism occurs as a rule in patients* with atrial fibrillation especially with mitral stenosis and not in patients with sinus rhythm (except as a result of myocardial infarction with mural thrombosis, bacterial endocarditis or rarely a thrombus on an aortic arteriosclerotic plaque). No embolization occurred during or after successful conversion of atrial fibrillation to sinus rhythm by quinidine in 119 cases reported by Yount et al.,[illegible] in 93 cases reported by Sokolow[155] and 44 by McMillan and Welfare.[14] The risk of quinidine toxicity may be minimized by proper administration of the drug and observation of the patient and is greatly outweighed by the dangers of persistent atrial fibrillation. *Anticoagulants* have been employed for two weeks before attempting conversion of atrial fibrillation[17, 155] with quinidine or Pronestyl and for a variable period after conversion.

Digitalis Therapy in Atrial Fibrillation

The *purpose* of digitalis therapy in atrial fibrillation is to slow the ventricular rate, not to restore sinus rhythm. Most of the circulatory disadvantages of atrial fibrillation are due not to the irregularity but to the rapid ventricular rate. *Digitalis should be first administered* to slow the ventricular rate when this is rapid. Then conversion to sinus rhythm may be attempted with quinidine while digitalization is maintained. However, overdigitalization should be avoided as it may interfere with the effectiveness of quinidine.

The *action* of digitalis in atrial fibrillation may be as follows: 1. By stimulating the *vagus nerve it may foster atrial fibrillation*. According to the theory of repetitive impulses from an ectopic center, digitalis is ineffective in restoring sinus rhythm because it does not diminish and may enhance myocardial excitability. 2. By direct action on the a-v node and bundle digitalis slows conduction. This prevents most of the excessive atrial impulses from reaching the ventricle

allows more time for ventricular diastolic recovery and filling and results in slower more forceful ventricular contractions Thus the digitalis vagal effect tends to maintain the fibrillation of the atria while the direct effect on the functional conduction system slows the ventricular rate But the disadvantage of the former is more than compensated by the benefit of the latter

The *dosage and methods of administering digitalis* have been described elsewhere in detail (p 259) In occasional very urgent situations it may be advisable to administer digitalis intravenously (Figure 79) Rapid digitalization may also be accomplished by a single oral dose of digitalis glycoside The therapeutic effect and subsequent dosage should be gauged by the cardiac rate as determined by auscultation at the apex and not by examination of the pulse Serial electrocardiograms are desirable but rarely essential It is desirable to reduce the apical heart rate to between 60 and 70 per minute at rest This may not be possible in the presence of complications or associated conditions causing fever or in the presence of hyperthyroidism After the desired ventricular rate is attained the subsequent daily dose necessary to maintain this rate should be determined In instances of persistent atrial fibrillation it may be necessary to continue the maintenance dose of digitalis indefinitely

The *toxic symptoms* of digitalis have been discussed elsewhere (p 264) Attention is called again in particular to anorexia nausea and vomiting diarrhea yellow vision bigeminal rhythm multifocal (bidirectional) premature ventricular contractions and heart block Bradycardia of 50 or less or regular nodal rhythm developing during digitalis medication usually denotes excessive dosage

Quinidine Therapy (Fig 80)

The use of quinine for the treatment of cardiac irregularities was introduced in recent years by Wenckebach [76] Quinidine a dextro-rotatory isomer of quinine was later introduced by Frey [77] and found to be more effective

The *purpose* of quinidine therapy in atrial fibrillation is to restore normal sinus rhythm Quinidine therapy designed to convert atrial fibrillation to sinus rhythm is especially indicated when (a) there is a history of previous arterial embolism (b) there is intractable heart failure or (c) there are symptoms of anxiety or distress directly attributed to the arrhythmia

Complete heart block is an absolute contraindication and bundle branch block or severe intraventricular conduction disturbance [redacted] usually accepted as a contraindication to quinidine therapy [redacted] The contraindication to using quinidine in cases with bundle branch

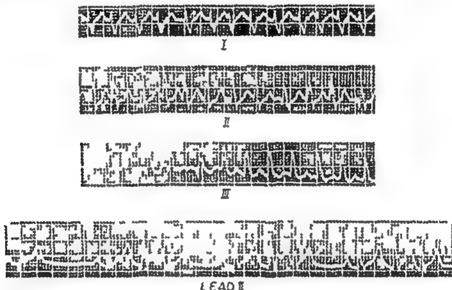
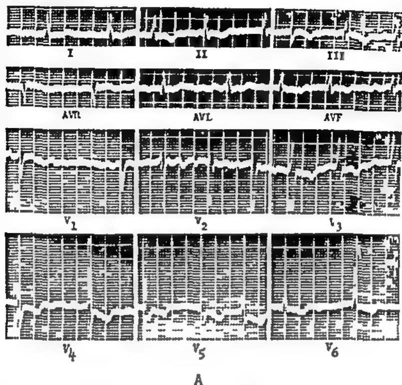


Fig 79 Paroxysmal atrial fibrillation in upper three strips Ventricular rate 210 per minute Lowest strip taken 1 hour after 0 8 mg of Cedilanid intravenously Sinus rhythm with trigeminy due to atrial extrasystoles

block is only relative since Goldman[87] reported the successful conversion of atrial fibrillation to sinus rhythm in 7 of 9 patients with bundle branch or intraventricular block. Many physicians have long regarded quinidine as not indicated or contraindicated in cases of chronic cardiac disease or heart failure, longstanding atrial fibrillation and cardiac enlargement, because of the tendency of atrial fibrillation to recur when it is abolished, because of the danger of embolization from atrial thrombi as sinus rhythm is restored, and because of the risk of sudden death from cardiac standstill.



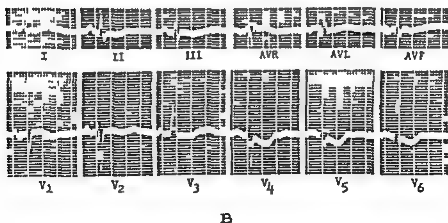


Fig 80 *A* Atrial fibrillation in a patient with mitral stenosis hypertension and recent cerebral embolism *B* Restoration of sinus rhythm after 2 gm of quinidine two days previously and 3 4 gm quinidine on preceding day

With increased understanding of the pharmacology and of the proper dosage and administration of the drug and with more objective control of dosage by direct writing electrocardiography and determinations of quinidine plasma levels these contraindi

cations have been greatly contracted and quinidine has been used more frequently to convert atrial fibrillation to regular sinus rhythm. Restoration of sinus rhythm has been variously reported in 50 to 89 per cent of cases or more.[156, 106, 188, 80, 189] Recently Brown and McMillan[30] reported restoration of sinus rhythm in 89 per cent of 67 patients with atrial fibrillation and congestive heart failure and virtually identical results were reported by Bedard.[14] A relapse occurred in 4 of 23 patients with rheumatic heart disease and in one of 35 patients with coronary heart disease. Sokolow[188] achieved restoration of sinus rhythm in 52 per cent of 94 cases of rheumatic heart disease and chronic atrial fibrillation and in 80 per cent of 85 non-rheumatic cases. In my experience the chances of success improve markedly in patients with rheumatic or coronary heart disease and enlarged hearts if the dosage of quinidine is increased to the point of moderate toxicity. Relapses most likely to occur in rheumatic heart disease should not exceed 20 per cent if adequate doses of quinidine are maintained.

The *action* of quinidine in atrial fibrillation is uncertain. The proposed explanation for the action of quinidine depends on one's advocacy of the circus movement theory or the theory of rapid impulses from ectopic foci as the mechanism of atrial fibrillation. According to the circus movement theory quinidine acts as follows in atrial fibrillation:

1. By direct action on the atrial musculature it prolongs the refractory period. Consequently, when the circus wave responsible for atrial fibrillation completes its circuit and finds the muscle still refractory, the circus movement is ended. This permits the sinoatrial node to reestablish itself as the pacemaker.

2. On the other hand, quinidine also slows the rate of impulse transmission (conduction). This tends to perpetuate the circus movement by allowing the tissue before the crest of the excitation wave more time to recover from its refractoriness. If the first effect (above) predominates, quinidine may abolish atrial fibrillation. If the second predominates, atrial fibrillation persists. The second effect also tends to slow the atrial rate. Consequently, atrial fibrillation is often converted to flutter before sinus rhythm is restored by quinidine.

According to the theory of rapid impulses from ectopic foci, the action of quinidine in atrial fibrillation is explained more simply.[1, 9] Quinidine depresses myocardial excitability and may lengthen the effective refractory period following contraction. It thereby diminishes the rate of impulse formation by an ectopic focus. When the rate is slowed to below the fibrillation threshold, atrial flutter usually ensues.[189] With further slowing or with inactivation of the focus, the sinoatrial node resumes its role as pacemaker. Success in converting atrial fibrillation to sinus rhythm is then determined on the one hand by the dose and plasma level of quinidine and on the other by the intensity of rapid impulse formation by the ectopic center. Failure to convert denotes inadequacy of quinidine dosage or excessive intensity of ectopic impulse formation. According to the circus movement theory, the success or failure of quinidine in restoring sinus rhythm is awkwardly attributed to predominant reduction in the refractory period when it succeeds and to predominant impairment in conductivity when it fails.

Quinidine tends to increase the ventricular rate, but this undesirable temporary effect is negligible if sinus rhythm is restored. The increased ventricular rate results from (a) the slowing of the atrial rate which allows better a-v conduction and (b) depression of the vagus nerve and therefore improved conduction of atrial impulses through the a-v node and bundle.

Thus quinidine is employed primarily in the hope that it will restore sinus rhythm by abolishing the ectopic focus or the circus rhythm. On the other hand, digitalis is employed with a view to slowing the ventricular rate by depressing a-v conduction; its effect on the atrial fibrillation, if any, is to foster it by shortening the refractory period or increasing atrial excitability.

Quinidine Plasma Levels. Recent studies have related proper dosage and administration of quinidine to quinidine blood plasma levels.[114, 190, 188, 8] Plasma quinidine concentration may be determined with the aid of the photofluorometer.[12] The control of arrhythmias is often dependent on attainment of a critical blood threshold level, which varies in different individuals but is reasonably constant in the same individual. The probability of controlling an arrhythmia increases

the higher the blood level. Therefore the dose of quinidine must be increased until the highest possible safe level as determined by symptoms, electrocardiographic signs and, if feasible, quinidine plasma concentrations, before conceding defeat in an effort to convert atrial fibrillation to sinus rhythm. However, in many patients restoration of sinus rhythm is accomplished with relatively small dosage and with plasma quinidine levels of 4 mg. per liter or less. Hence, dosage of quinidine should be raised gradually.

Following a single oral dose of 0.4 to 0.6 gm., quinidine is detected in the blood in one hour, usually reaches its peak in two or three hours and thereafter diminishes.[114] Approximately one-half the dose is dissipated in eight hours but some of the drug is still present after 24 hours. More than 90 per cent of the quinidine is usually eliminated in the urine in 24 hours. Since the peak concentration is usually attained in two hours, effective cumulation is accomplished by administering multiple doses orally every two hours. Furthermore, after five or six doses at two hour intervals—a common method of administration—about 40 to 50 per cent of the peak concentration is still present 12 hours after the last dose. Consequently, repetition of such a dose schedule on two or three successive days effects a progressive elevation of plasma quinidine level even without increase in the individual dose. Impaired renal function and severe congestive heart failure[11] may result in disproportionately high plasma quinidine concentration for a given dosage.

Often atrial fibrillation will be converted to regular sinus rhythm and sinus rhythm will be maintained when the plasma quinidine concentration ranges between 4 to 6 mg. per liter. This level can usually be attained by doses of 0.4 to 0.6 gm. four times daily. Sokolow[113] was successful in converting atrial fibrillation to sinus rhythm in 82 per cent of 119 attempts in 111 patients with a mean plasma quinidine level of 5.4 mg. per liter (usual range 4 to 8 mg. per liter) on a regimen of 0.4 to 0.6 gm. every two hours for five doses daily. However, persistent atrial fibrillation often cannot be converted until the plasma level reaches 8 to 10 mg. per liter. Thereafter, sinus rhythm may be maintained with lower quinidine concentrations. Vomiting, diarrhea, mild tinnitus and mild prolongation of intraventricular conduction may occur at blood levels between 4 and 6 mg. per liter but serious toxic disturbances are infrequent unless the plasma concentration exceeds 8 or 9 mg. per liter.

Administration of Quinidine in Atrial Fibrillation

Oral Administration. One or two doses of 0.2 gm. (3 grains) each may be given an hour apart to test for sensitivity. This is done as a matter of custom; its value is uncertain. Subsequent dosage has not become standardized since occasional patients experience a favorable response with one or two small doses while others require the maximal dosage that can be tolerated. As a rule I prescribe 0.3 gm. (5 grains) every two hours for six to eight doses, discontinuing when the patient is asleep at night. This dosage is repeated the following day if the arrhythmia persists. Thereafter, if unsuccessful and if there are no toxic symptoms (see below, p. 369), I increase the dosage progressively (0.4 gm. every two hours for six doses the following day, then 0.6 gm. every two hours for five doses the next day, and finally 0.8 gm. every two hours for five doses if tolerated). If this fails it is rarely desirable or effective to exceed 4 gm. daily. In fact, if 0.6 gm. every two hours for six doses do not restore sinus rhythm, larger doses rarely succeed.[7] When more than 2 gm. daily is given, serial electrocardiograms should be taken to observe whether excessive prolongation of intraventricular conduction occurs due to quinidine toxicity. As a rule, toxic symptoms appear when more than 3.0 gm. is given daily and it is difficult to increase the dose beyond 4 gm. daily because of toxic symptoms or signs.

Many variations of the above schedule may be followed. One may also administer 0.4 gm. of quinidine every four hours day and night for two to four days until sinus rhythm is restored or significant toxicity is evident. This mode of administration may be improved by the use of delayed absorption coated pills taken at bedtime to eliminate the need for a dose during the sleeping hours.[171] Another method is to give 0.2 or 0.4 gm. of quinidine four times daily for 72 hours. If this is ineffective, the dose is increased by 0.2 gm. every 72 hours. Thus if one begins with 0.4 gm. four times daily, the patient receives 0.6 gm. four times daily by the fourth day, 0.8 gm. four times daily by the seventh day, and so on. In mild arrhythmias 0.3 gm. (5 grains) three or four times daily may suffice. Occasionally a

single large daily dose is effective when multiple doses at regular intervals are not. In the series reported by Brown and McMillan[20] in which conversion to sinus rhythm was effected in 89 per cent of cases, the average total dose of quinidine was 2.8 gm (range 1.8 to 4.2 gm) in patients with rheumatic heart disease and 2.5 gm (1.2 to 5.4 gm) in patients with atherosclerotic heart disease.

Sometimes it becomes necessary to discontinue quinidine before atrial fibrillation has been converted to regular sinus rhythm. But it should be emphasized that a high percentage of success will be attained only at the expense of moderate toxicity in many patients. Tolerable nausea and vomiting, slight tinnitus and slight degrees of widening of the QRS complex are not necessarily contraindications to further doses of the drug. The drug should be discontinued if the QRS complex is widened to 0.14 second or more, if the P wave disappears or there are frequent ventricular premature beats or ventricular tachycardia, or if there are other evidences of toxicity listed below. It should also be discontinued if the quinidine plasma concentration is more than [illegible] mg per liter.

Note that a given regimen of quinidine administration may fail at one time, yet succeed at a later day. Marked nervous tension, infection or fever from any cause, pulmonary or myocardial infarction, digitalis toxicity and severe heart failure are among the factors which have been noted to interfere with the effectiveness of quinidine. When time or treatment have controlled these inhibiting factors, a course of quinidine should be repeated and this will often succeed despite previous failure.

Maintenance of Quinidine. When regular sinus rhythm is established, maintenance doses of quinidine are continued, usually beginning with 0.4 gm four times daily. McMillan and Welfare[14] found the average maintenance dose 0.28 gm every six hours. Larger or smaller doses are given according to the dose required for conversion. If sinus rhythm persists for several months, the maintenance dose may be gradually reduced and even discontinued eventually. If there is a recurrence of atrial fibrillation, conversion may be attempted by the original doses which were effective.

Intravenous Administration of Quinidine. Very rarely the urgency of a situation may demand that quinidine be given parenterally, e.g., in some cases of ventricular tachycardia.

Quinidine gluconate is available in 10 cc rubber stoppered ampules containing 0.8 gm of the quinidine salt or 0.5 gm of the anhydrous quinidine. This is administered intravenously very slowly until the desired effect is obtained. The usual dose is 0.3 to 0.8 gm (4 to 10 cc). Greater safety and better control of dosage are obtained by diluting the ampule of quinidine gluconate in 50 to 150 cc of 5 per cent glucose solution and administering the solution at about 2 to 5 cc (25 mg) per minute. Frequent electrocardiograms should be taken during the infusions.

Quinidine hydrochloride (Brewer) is available in 2 cc ampules containing 0.6 gm for intravenous or intramuscular use. *Quinidine lactate* (Lilly) is also supplied in ampules of 0.65 gm dissolved in 10 cc of sterile saline.

Intramuscular Administration of Quinidine. Quinidine gluconate may be effectively employed by intramuscular administration. Since a definite response may be obtained in 15 minutes or less and a maximum effect in 1 to 2 hours, intramuscular administration is preferable to intravenous, even when speed is important, except in the most urgent situations. Intramuscular quinidine is also indicated when the patient is unable to take oral medication or absorption is uncertain, i.e., in the presence of intense nausea, vomiting, diarrhea, stupor or shock. Five cc (0.4 gm) of the quinidine gluconate is administered intramuscularly and may be repeated once or twice at two to four hour intervals until the desired effect is obtained or toxic manifestations compel discontinuation.

Quinidine is also indicated in the treatment or prevention of various types of premature beats (p. 341), atrial flutter (p. 357), atrial tachycardia (p. 350) and ventricular tachycardia (p. 374), except when the latter is associated with Adams-Stokes syndrome.

Toxic Effects of Quinidine. Quinidine is a toxic and sometimes dangerous drug which must be administered with special care. It is therefore advisable that the patient be under close supervision. If large doses are given, serial electrocardiograms are desirable.

Among the *toxic symptoms* are those known as cinchonism, caused not only by the cinchona alkaloids but also by salicylates and cinchophen. These symptoms with mild intoxication include tinnitus, impaired hearing

headache, nausea, mild diarrhea or a slight disturbance in vision. Vomiting, diarrhea and slight tinnitus are the commonest symptoms with effective quinidine dosage. With more advanced toxicity, tinnitus and hearing impairment become more severe; there is a blurring of vision, disturbed color perception, photophobia and diplopia (quinine amblyopia or amaurosis);[16] nausea, vomiting, diarrhea and abdominal pain are frequent; the skin becomes hot and flushed and urticarial, macular or papular eruptions occur. Severe cerebral symptoms may develop, ranging from headache to fever, confusion and delirium. I have observed a patient in whom a single dose of quinidine given orally was followed on several occasions by chills and fever within two hours and then by purpura and melena. Fever[17, 191] or thrombocytopenic purpura[16, 195] due to quinidine has since been reported by various observers.

Respiratory distress, cyanosis, dizziness and cold sweat, convulsions and collapse may result from quinidine idiosyncrasy.[19] Convulsions may result from direct action on the cerebral cortex or from the production of cardiac asystole but are extremely rare.

A serious *tachycardia* associated with atrial flutter may follow treatment of atrial fibrillation by quinidine. This is less likely to occur if quinidine is given after previous digitalization.

Electrocardiographic Changes and Cardiac Complications of Quinidine. *Intraventricular conduction defect* with widening of the QRS to more than 0.12 second, cardiac standstill, ventricular tachycardia[209] and ventricular *fibrillation*[9] *may result from the depressant* effects of quinidine on the cardiac musculature and conduction system. A prolongation of the Q-T interval occurs early and increases with augmented dosage. However, this does not necessarily indicate toxicity. The prolonged Q-T interval may be due to a prominent U wave, widening of the QRS or both.[298] Depression of the ST segment, low voltage of T waves, widening and notching of the P wave are other electrocardiographic changes which may occur *even with therapeutic doses of* quinidine. Atrioventricular and bundle branch block are common with toxic doses. Marked widening of the QRS to 0.16 to 0.20 second or more may presage impending ventricular tachycardia or fibrillation. Sudden death following quinidine therapy is more apt to be due to cardiac standstill (depression of the sino-atrial and a-v nodes) or to ventricular tachycardia and ventricular fibrillation[9, 1] than to embolization. It may also result from respiratory paralysis. When collapse follows quinidine, revival of the heart is most apt to be effected by the administration of epinephrine or norepinephrine.[71]

All these symptoms and signs should be excluded by careful questioning and examination *before each new dose of the drug is given*. Serial electrocardiograms should be taken when large doses of quinidine are given or when the drug is administered for long periods. Occasionally, mild symptoms may have to be tolerated if the arrhythmia is sufficiently disturbing and is controlled only by *slightly* toxic doses of quinidine. Otherwise the drug should be discontinued when symptoms of intoxication are discovered.

Treatment of Atrial Fibrillation with Procaine Amide (Pronestyl)

Procaine amide (p. 340) is effective in converting many cases of atrial fibrillation to sinus rhythm[176, 166, 173, 67] and should be employed if quinidine cannot be tolerated or is ineffective. Schack and associates[173] restored sinus rhythm in 17 of 21 patients with atrial fibrillation of less than one week's duration, in 15 of 25 patients with atrial fibrillation for more than one week but less than three years, but in only 3 of 15 patients with the arrhythmia for more than three years. Digitalization is first instituted to slow the ventricular rate. Then 1 gm. (4 capsules) of the procaine amide is given orally every three or four hours for six doses or until sinus rhythm is restored. *Usually a total of 3 to 6 gm. are required*. If this dose is ineffective, it is improbable that conversion to sinus rhythm will be accomplished. Procaine amide may also be administered intramuscularly or intravenously in 500 to 2000 mg. doses (p. 375).

Maintenance therapy consists of 0.5 gm. orally every six hours. Attempts may be made to reduce and discontinue the drug after two or more weeks of sinus rhythm. Toxic effects (*see also p. 341*) *include electrocardiographic* changes (such as lowering of the voltage of QRS and T waves, widening of QRS and QT), nausea, vomiting, choking sensations, diaphoresis, malaise or prostration.

Anticoagulant Therapy

Oral anticoagulants (p. 577) may be uti-

lized for a period of two weeks prior to the employment of quinidine or Pronestyl and for a variable period thereafter in an effort to prevent embolization due to changing rhythm Oral anticoagulant therapy for prolonged periods has also been advocated in patients with atrial fibrillation and emboli, even when no effort is made to convert the arrhythmia to sinus rhythm Claims that the incidence of embolism is reduced[48] are difficult to evaluate

Treatment of Paroxysms

Treatment of a paroxysm of atrial fibrillation is indicated only if it is associated with distressing and prolonged palpitation evidences of heart failure or of cerebral or peripheral ischemia Specific treatment is usually unnecessary when symptoms are mild or absent when the attack is of very brief duration or when it is symptomatic of some underlying disease such as hyperthyroidism pneumonia surgical procedures etc In the latter circumstances treatment is directed only to the underlying disease for the arrhythmia subsides spontaneously or with cure of the basic cause

When specific treatment of the arrhythmia is necessary digitalis quinidine or procaine amide (Pronestyl) may be administered as described above for established atrial fibrillation As a rule I first digitalize the patient rapidly to slow the ventricular rate Often sinus rhythm reappears very soon even before quinidine is started Otherwise I administer quinidine or if this is not readily effective I employ Pronestyl orally Pronestyl has been found to be more effective in paroxysmal than in established atrial fibrillation (For dosage and methods of administration see digitalis p 259 quinidine p 368 and procaine amide (p 340) Atabrine (0 4 gm intramuscularly) may be tried if these fail [83, 37]

Prevention of Attacks

Quinidine is usually employed to prevent attacks of atrial fibrillation which recur frequently and produce distressing symptoms It is impractical to take this drug continuously when attacks occur rarely When indicated the quinidine may be given in doses of 0 2 gm (3 grains) three times daily and increased progressively in dosage and frequency until the attacks no longer recur or symptoms of toxicity appear But it is rarely justifiable to take more than a maximum of 3 gm daily (divided in six to twelve doses) If the patient discovers that the attacks occur at definite times during the day or night or under special circumstances, a dose of quinidine sulfate 0 2 to 0 4 gm (3 to 6 grains) may be taken one to two hours prior to the time the attack is anticipated Such extra doses at critical times may be used also to supplement the regular schedule of quinidine Long acting quinidine tablets taken before retiring are useful to prevent nocturnal attacks

If quinidine proves ineffective in preventing frequent and annoying paroxysms the patient should be digitalized (p 259) and kept on maintenance doses of digitalis This regime is designed not to prevent attacks but to restrain the ventricular rate to below 100 per minute if and when the attack should recur However this objective is not usually attained

VENTRICULAR TACHYCARDIA

Ventricular tachycardia is a rapid regular rhythm in response to stimuli arising in an ectopic focus or ring in the ventricular conduction system [80] Usually the tachycardia occurs in brief paroxysms lasting minutes or hours but occasionally it persists for weeks or months (Dubbs and Parmet [81] 21 days Freundlich [74] 26 days May [135] 77 days) Gallavardin[83] has described a form of ventricular tachycardia recurring in very brief paroxysms and characterized by runs of ventricular extrasystoles separated by one two or several sinus beats

Mechanism

The mechanism of ventricular tachycardia is probably similar to that of atrial tachycardia (p 344) except that the ectopic focus or ring is situated in the ventricle instead of in the atrium The tachycardia is then visualized as a series of rapid rhythmic premature beats arising in this ectopic focus or in response to a similar series of circus movements in a ventricular ring of tissue [82]

Experimentally ventricular tachycardia has been produced by ligation of a coronary artery by the administration of barium chloride by application of aconitine [175] by electrical stimulation[151] and by combined stimulation of the vagus and accelerator nerves [143] Chloroform and cyclopropane anesthesia predispose to the production of ventricular tachycardia by epinephrine [107, 111]

The ventricular rate varies usually between

150 and 250 but may be as rapid as 300 per minute. Sometimes the atria contract regularly and independently in response to the normal sinus impulse while the ventricles respond to the ectopic ventricular stimulus. However, the atria may also respond to the ventricular stimulus which may be conducted backward (retrograde conduction) along the bundle branches, a-v bundle and node. Since retrograde conduction is more difficult than normal downward conduction along the bundle and since the rate of ventricular impulse formation is excessive, various degrees of ventricular-atrial block may occur. In this respect ventricular tachycardia resembles atrial flutter with a reversal in origin and direction of the controlling impulse.

The Electrocardiogram

The electrocardiogram of ventricular tachycardia is characterized by (Figs. 81, 82):

1. *QRS complexes with approximately regular rhythm which are slurred and widened at rates of 150 to 200 or more per minute.* The configuration of the QRS is that of a left or right ventricular premature beat, or the complexes may be alternatingly bidirectional. The latter is most often associated with digitalis intoxication[2,4,100] and severe myocardial damage. The change in direction has been attributed to cardiac control by two independent ventricular foci or to a single ectopic impulse, possibly at the bifurcation of the bundle of His, which is transmitted alternately over the left and right bundle branches because of a defect in conduction. Before and after the paroxysm one may find isolated ectopic ventricular complexes with the same form as that seen during the paroxysm.

2. The P waves are usually undisturbed in their sinus rhythm but are often obscured by the ventricular complexes. Esophageal or right precordial leads may disclose the P waves at a slower rate than ventricular systoles. When 1:1 retrograde conduction occurs, the P waves may be observed abnormal in contour and superimposed on the T waves or following them. P waves are often less frequent than QRS complexes owing to retrograde partial heart block (dropped atrial beats).



Fig. 81. Paroxysmal ventricular tachycardia. Lead I. A brief paroxysm preceded and followed by sinus beats. Abnormal configuration QRS complexes denoting ectopic focus but all from same site. Slower rate and slight irregularity of R-R cycles in contrast with regularity in atrial tachycardias.

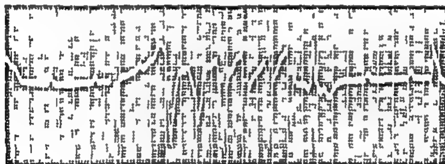


Fig. 82. Ventricular tachycardia in complete heart block associated with Adams-Stokes syndrome. Attacks accentuated by administration of epinephrine.

Occasionally atrial fibrillation or atrial tachycardia accompanies paroxysmal ventricular tachycardia but this must be distinguished from atrial flutter or fibrillation with bundle branch block. Ventricular tachycardia may be associated with a-v dissociation or complete heart block.

Following subsidence of a paroxysm of ventricular tachycardia the T waves may be inverted for a few hours or days, possibly due

to myocardial fatigue or ischemia occasioned by the tachycardia [194] The electrocardiographic pattern seen after a paroxysm of ventricular tachycardia may closely simulate that of acute myocardial infarction [74] This similarity is heightened when the paroxysmal tachycardia is accompanied by intense precordial oppression or pain The differentiation can usually be made by a consideration of the history and ancillary clinical findings (Chapter 21)

Occasionally the electrocardiogram of ventricular tachycardia may be confused with that of atrial tachycardia and intraventricular conduction disturbance or with atrial flutter and 1 1 block or with atrial fibrillation with aberrant ventricular complexes [1, 196] Ventricular tachycardia may be distinguished in a long strip of the electrocardiogram by the finding of isolated premature ventricular beats with the same QRS configuration before or after the paroxysm or by the discovery of P waves in abnormal relationship to the QRS complex and at a slower rate or by the occurrence of occasional transitional ventricular complexes resembling sinoatrial beats [80]

Ventricular flutter is characterized by rapid uniform and virtually regular oscillations usually at the rate of 250 per minute or more The complexes differ from those of ventricular tachycardia in the absence of distinct QRS and T waves or a blending of the two in ventricular flutter The latter is distinguished from ventricular fibrillation in that the undulations are irregular in size shape and rhythm

Etiology

Paroxysmal ventricular tachycardia is most often associated with recent myocardial infarction but it may occur also with hypertensive and coronary heart disease or rheumatic heart disease It has followed the administration of excessive amounts of digitalis [75] quinidine [69] or Pronestyl and has resulted from potassium intoxication [1, 5] *Ventricular tachycardia due to digitalis may be* characterized by bidirectional ventricular complexes [274, 100] A relationship of ventricular tachycardia to emotional strain and fatigue has been postulated [18] Ventricular tachycardia may occur without apparent organic heart disease In a review of 107 cases of paroxysmal ventricular tachycardia Armbrust and Levine[7] noted that the arrhythmia was associated with coronary heart disease in 74 per cent with rheumatic heart disease in 8 4 per cent and with apparently normal hearts in 12 per cent Furthermore there were 5 instances of serious or fatal paroxysmal ventricular tachycardia complicating the W-P W syndrome But these may have represented instances of atrial tachycardia or fibrillation with conduction through an anomalous atrioventricular bundle Wilson et al [217] described a clinical type of ventricular tachycardia apparently induced by exertion Orthostatic paroxysmal ventricular tachycardia has also been described [188]

Ventricular tachycardia as well as other arrhythmias occurs relatively frequently in the course of human cardiac catheterization[88] and surgical operations especially those involving manipulation of the heart and great vessels But they appear also in the course of various thoracic or other operations [110, 35] The arrhythmias occur not only because of direct mechanical cardiac irritation but also as a result of anoxia and vagal reflexes associated with the anesthesia and the operation

Symptoms and Signs

The variable clinical forms of ventricular tachycardia have been classified by Froment et al [71] into a number of categories including (1) terminal prefibrillatory tachycardia occurring in association with serious underlying disease and always fatal (2) ventricular paroxysmal tachycardia due to lesions of the septum caused by coronary occlusion or syphilis (3) less serious forms of ventricular tachycardia in apparently healthy hearts The subjective symptoms are identical with those described under atrial paroxysmal tachycardia (p 346) Essentially these are attacks of palpitation starting and stopping suddenly lasting from a few minutes to many hours with mild to moderate dyspnea and occasionally dizziness faintness or syncope due to cerebral ischemia caused by a deficient cardiac output Occasionally there is little or no subjective distress even when as in a case described by Freundlich [76] the tachycardia persisted for 26 days

Paroxysmal ventricular tachycardia occurring in patients with heart block may be complicated by ventricular fibrillation ventricular arrest and the Adams Stokes syndrome [1, 157] (Fig 83) Not infrequently substernal and precordial pain identical with that of angina pectoris may appear at the onset of the tachycardia When the pain is

severe and persistent, it closely resembles that of acute myocardial infarction When ventricular tachycardia complicates acute myocardial infarction it is often associated with the clinical picture of shock Congestive heart failure is likely to occur with ventricular tachycardia especially if the attack is prolonged and there is serious underlying heart disease

Examination discloses an apical and pulse rate of 160 to 180 but occasionally as high as 200 to 300 per minute Although the rhythm is regular prolonged auscultation of the heart may disclose slight irregularity as well as corresponding differences in the quality or intensity of the first sound[197] (But cf. also MacKinnon[198]) The latter is due to varying relationships of the atrial and ventricular contractions in different cycles and therefore to differences in the position of the atrioventricular valve cusps which determine the character of the first heart sound Occasionally only one heart sound is heard with each beat

The jugular veins may, as in atrial tachycardia, show prominent regurgitation ("a") waves due to the occurrence of atrial contraction, while the tricuspid valve is closed by simultaneous ventricular systole There are fewer jugular pulsations than apical heart beats

Other symptoms and signs often present are due to an underlying acute myocardial infarction, to digitalis intoxication or to the heart failure which necessitated the use of digitalis

Diagnosis

For diagnosis and differential diagnosis of the tachycardias, see page 378

Prognosis

Ventricular tachycardia, unlike atrial tachycardia, is usually a serious condition, partly because of the frequency of an underlying myocardial infarction and partly because it may be the harbinger of a fatal ventricular fibrillation Ventricular tachycardia with alternating direction of the ventricular complexes has been considered especially ominous and almost invariably fatal But recoveries have been observed with appropriate treatment whether the direction was unidirectional or bidirectional[16] Zimmerman[203] treated 8 of 10 cases of ventricular tachycardia with quinidine with recovery in 7 of them Ventricular tachycardia may persist for many days or weeks[204] In general the prognosis of ventricular tachycardia, as of most arrhythmias depends on the absence or presence of underlying cardiac disease and on the outlook presented by that disease The prognosis is generally favorable in those without apparent heart disease

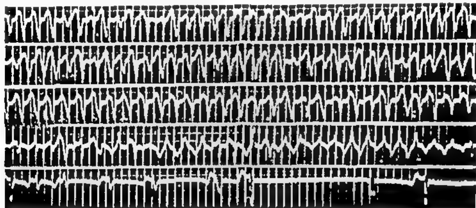


Fig 83 Ventricular tachycardia followed by prolonged ventricular standstill and Adams-Stokes syndrome

Treatment

Quinidine and procaine amide are the most effective drug Both depress myocardial excitability They are both contraindicated when ventricular tachycardia is associated with heart block and Adams-Stokes syndrome Under these circumstances Isuprel should be administered subcutaneously[115] or sublingually[181] (p 393)

Quinidine in Ventricular Tachycardia Quinidine effectively restores normal rhythm in the majority of cases For details of quinidine administration see page 368 Oral administration is preferred except in extreme emergency, the dosage is that which accomplishes the desired result without serious toxicity Commonly,

after a test dose of 0.2 gm. (3 grains) 0.3 gm. is administered every 2 hours for 6 doses. This dose is increased daily to 0.4 gm., etc., as described under atrial fibrillation (p. 368). Maintenance doses, varying from 0.3 gm. (5 grains) three times daily to 0.6 gm. four or five times daily, may be required for several days or longer to prevent a recurrence.

Occasionally quinidine must be given intravenously[41, 109] or intramuscularly for extreme emergency or urgent haste, or because the patient is vomiting and unable to take oral medication. Quinidine gluconate, lactate or hydrochloride may be employed for intravenous or intramuscular injection. Quinidine gluconate is administered very slowly intravenously until sinus rhythm is restored or toxic effects appear or up to a total of 0.8 gm. (10 cc.). Or the 10 cc. ampule may be diluted in 50 to 150 cc. of 5 per cent glucose in distilled water and given by slow drip in 30 minutes to an hour. Quinidine gluconate may also be given intramuscularly (0.4 to 0.8 gm., i.e., 5 cc. to 10 cc.) and repeated several times if necessary at two hour intervals. Frequent electrocardiograms are desirable to avoid toxic effects and to evaluate the effectiveness of quinidine therapy.

Procaine Amide (Pronestyl) in Ventricular Tachycardia[115, 185, 4] Pronestyl is as effective as quinidine in the treatment of ventricular tachycardia and may be preferable to quinidine when the urgency of the situation indicates the need for intravenous administration, or when the ventricular tachycardia is due to digitalis toxicity. Pronestyl may be effective after quinidine has failed[108] and vice versa. The usual recommended intravenous dose is 100 to 200 mg. per minute up to a total of 2 gm., but the possibility of hypotension may be minimized by even slower administration, e.g., at the rate of 100 mg. in five minutes, with frequent determinations of the blood pressure. For slow intravenous infusion 1 or 2 gm. of procaine amide is dissolved in 100 or 200 cc. of 5 per cent glucose in distilled water and administered at the rate of 2 to 3 cc. per minute. As with quinidine, concomitant electrocardiographic observations are desirable. All of seventeen episodes of persistent paroxysmal ventricular tachycardia in 13 patients treated with Pronestyl intravenously were terminated by doses ranging from 300 to 2500 mg.[114] Seven of these required more than 1000 mg. The intravenous infusion is discontinued as soon as regular sinus rhythm is restored or if marked widening of the QRS or P-R interval appears.

The most serious complications of intravenous Pronestyl therapy are marked widening of the QRS complexes, convulsions and hypotension.[193] The hypotension may be combated by slowing or stopping the injection, or by administering norepinephrine (Levophed) intravenously[179] (p. 563). The administration of 100 mg. of phenobarbital sodium intramuscularly before starting the intravenous Pronestyl has been advocated to prevent possible convulsions.[154]

Procaine amide is also rapidly effective when administered *intramuscularly* and usually obviates the need for intravenous injection. Peak levels of Pronestyl may be attained within fifteen minutes to an hour.

The intramuscular dose of Pronestyl is 0.5 to 1.0 gm. (5 to 10 cc.) initially. It may be repeated every two or three hours for several doses if the previous doses are ineffective.

Procaine amide may be given orally if there is no urgency. One gram (4 capsules) is given initially and repeated in two hours. If sinus rhythm is not restored, 0.5 to 1.0 gm. may be given thereafter at four to six hour intervals. A maintenance dose of 0.5 gm. every four hours may be desirable to prevent recurrence. The toxic effects of Pronestyl have been discussed (p. 341).

Other measures have been successfully employed to stop attacks of ventricular (and atrial) paroxysmal tachycardia. *Magnesium sulfate* in 20 per cent solution may be given intravenously, the first 5 cc. very slowly and then an additional 5 to 10 cc. if there are no ill effects and if the arrhythmia persists.[8, 100] *Calcium chloride* or *gluconate* has been reported to be effective when given intravenously in 10 per cent solution (10 to 20 cc. equals 1 to 2 gm.). *Potassium salts* (the chloride, acetate or iodide) have been given orally in doses of 1 to 5 gm. (15 to 75 grains) two to six times daily to decrease the frequency of attacks,[170] especially when ventricular tachycardia is due to digitalis toxicity. In one case in which the arrhythmia failed to respond to all of the above measures, sinus rhythm was restored and heart failure eliminated following the intramuscular injection of 0.4 gm. of atabrine. Samia and Alimuring[183] more recently reported a similar experience with a case of ventricular tachy-

cardia unresponsive to Pronestyl and quinidine in which sinus rhythm was restored after five oral doses of quinidine 0.3 gm each at two hour intervals. The intravenous injection of 10 to 20 mg of morphine sulfate repeated if necessary in a half to two hours has been advocated.

Although digitalis has generally been regarded as contraindicated in ventricular tachycardia, benefit has been reported when the drug was employed in cases not associated with digitalis toxicity or myocardial infarction. Digitalis may be dangerous in ventricular tachycardia complicating acute myocardial infarction because of increased myocardial irritability and the consequent hazard of inducing ventricular fibrillation.[69]

VENTRICULAR FIBRILLATION

Ventricular fibrillation is an extreme arrhythmia characterized by rapid irregular uncoordinated and ineffective twitchings of the ventricles.

In animals ventricular fibrillation may be induced by electrical stimulation (faradization) as was first demonstrated in Ludwig's laboratory in 1850.[104] But it may also be induced experimentally by coronary artery ligation, mechanical irritation, drugs such as barium chloride, calcium chloride, digitalis or epinephrine in excessive dosage. Chloroform and cyclopropane anesthesia are predisposing factors. It will be noted that many of these factors have been mentioned as capable of producing ventricular tachycardia. In fact ventricular premature beats, ventricular tachycardia and ventricular fibrillation are not an uncommon sequence in both experimental and human fibrillation of the ventricles.

Mechanism

The responsible mechanism, as in atrial fibrillation, is either an irregular or inconstant circus movement or an ectopic focus or foci with very rapid repetitive stimuli. According to Wiggers[1, 213] fibrillation starts with a premature beat from an ectopic focus or ring in the ventricle and is followed by circus movements involving smaller and smaller rings of myocardium, each of which develops independent excitations. This produces relatively ineffectual fractionate muscular contractions which become weaker and weaker as the coronary blood flow diminishes. The circulatory effects of ventricular fibrillation are much more serious than those of atrial fibrillation, for cardiac contraction becomes so ineffective that it is tantamount to asystole. The stroke output is annihilated and syncope and death follow.

The Electrocardiogram

The electrocardiogram exhibits rapid regular or irregular oscillations representing bizarre QRS complexes (Fig. 84). One type of

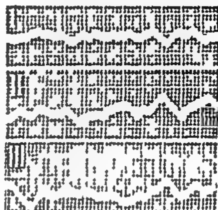


Fig. 84. Ventricular fibrillation in a fatal paroxysm of Adams-Stokes syndrome.

oscillation is fairly uniform with an amplitude of 8 to 10 mm. and a frequency of 130 to 300 per minute, which may gradually diminish as asphyxia develops.[11] This type has no isoelectric interval and is sometimes called ventricular flutter. In a second type the oscillations are irregular, somewhat more rapid and vary in amplitude (from 3 to 18 mm.), width and configuration. Terminally, ventricular fibrillation is characterized by completely irregular waves of low voltage or mere irregular undulations. There is usually complete or partial heart block and established a-v dissociation, or there may be sinus rhythm. In any event the atria continue their regular rhythm and usual rate until asphyxia develops.

The attack of ventricular fibrillation is usually introduced by an acceleration of the basic ventricular rhythm, always by "initial" premature beats, and often by short runs of irregular ventricular oscillations.[11] Impending ventricular fibrillation may be suggested by prefibrillatory phenomena characterized successively by (a) a labile basic ventricular rate, (b) the appearance of premature ventricular beats singly and in groups and (c) the appearance of bizarre ventricular com

plexes.[154] During the attacks there may be short or long asystolic pauses followed by a recurrence of the irregular rhythm of fibrillation or a return to the dominant rhythm (usually sinus rhythm with heart block) with occasional ventricular premature beats.

Etiology

In humans ventricular fibrillation may occur following acute cardiac infarction, in the course of heart block with Adams-Stokes syndrome, during surgical procedures under general anesthesia, following electrocution or lightning shock, after toxic doses of digitalis,[illegible] acetylstrophanthidin,[illegible] quinidine or Pronestyl, or as a terminal event in a variety of diseases usually after a more or less brief period of ventricular tachycardia. Since ventricular fibrillation is discovered accidentally and only by means of the electrocardiograph, it is uncertain how many unexplained and sudden deaths result from ventricular fibrillation.[196] Although the available experimental and clinical observations indicate that myocardial anoxia or necrosis[96] or certain toxic disturbances are chiefly responsible for initiating ventricular fibrillation, the exact mechanism is uncertain.

Clinical Aspects

Ventricular fibrillation is usually viewed as a terminal and terminating incident in certain instances of sudden death listed above under etiology, in all of which there may be insufficient anatomic change to account for the fatality. Ventricular fibrillation may also occur as a terminal incident in diseases which in themselves represent adequate causes of death.

Of more practical importance are the cases in which ventricular fibrillation is not soon fatal but occurs in transient paroxysms from which the patient recovers for a variable period of time. I have seen several patients suffer such attacks over a period of months, while another experienced innumerable ones over a period of 48 hours. Recovery from ventricular fibrillation following acute coronary occlusion has been reported.[51] Recovery may occur after absence of the heart beat for as long as five minutes.

These paroxysms are exhibited clinically as attacks of Adams-Stokes syndrome (p. 390) with syncope and convulsions indistinguishable from those due to ventricular standstill.[18] The fruitless ventricular twitches without mechanical expulsion of blood result in periods of asystole which are identical in effect with those due to ventricular standstill. Faintness occurs when ventricular fibrillation lasts 3 seconds or more, syncope after 10 to 20 seconds, and convulsions, apnea and incontinence after 40 seconds (average figures).

Treatment

When ventricular fibrillation is characterized by virtual asystole, sudden disappearance of heart sounds and blood pressure, treatment is that discussed under cardiac arrest (p. 1110). Essentially it consists of immediate thoracotomy, defibrillation[illegible] and restoration of the heart beat by cardiac massage. Oxygenation of the heart is maintained by cardiac massage and artificial respiration until the heart can be defibrillated. Ventricular fibrillation lasting for at least ten minutes has been abolished by electric shock.[17] Mouth to mouth breathing is carried out or oxygenation is maintained by a mechanically controlled respiration supplying 100 per cent oxygen under pressure. During this artificial respiration an alternating current is passed momentarily through two electrodes placed on the anterior and posterior aspect of the heart, in the form of one or more shocks at one second intervals ("serial defibrillation").[illegible] The development of a combined external cardiac pacemaker and defibrillator gives promise of carrying out both defibrillation and resumption of cardiac contraction without thoracotomy.[164]

When ventricular fibrillation occurs in transient paroxysms and when sinus rhythm is known to have been present before or between the paroxysms, Pronestyl or quinidine may be administered intravenously or intramuscularly as described above (p. 375). But quinidine and Pronestyl are contraindicated when the ventricular fibrillation occurs in patients with complete heart block and Adams-Stokes syndrome[188] (p. 393). In such cases the drug of choice is probably Isuprel (isopropylnorepinephrine)[150, 161] which is administered sublingually in 15 mg. doses every two hours or as required to control and prevent the attacks. It may also be administered subcutaneously in doses of 0.2 mg. Hydroxyamphetamine (Paredrine) in doses of 20 to 60 mg. every two to four hours orally may be used to prevent recurrence of the attacks.[150]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF TACHYCARDIAS

Regular Tachycardias

The tachycardias may first be segregated according to whether the rhythm is regular or irregular. If regular, the tachycardia may be sinus tachycardia, atrial, nodal or ventricular paroxysmal tachycardia or atrial flutter. A sudden onset and cessation of palpitation and tachycardia and the history of similar paroxysms is characteristic of the paroxysmal tachycardias and flutter but not of sinus tachycardia. If the heart rate exceeds 160 and especially if it is between 180 and 200 per minute, the disorder is usually a paroxysmal tachycardia, most commonly atrial. Sinus tachycardia and atrial flutter are associated with rates below 160 per minute, although the latter usually exceed 250 per minute when there is 1:1 atrioventricular conduction. Tachycardias with regular rhythm occurring in paroxysms lasting beyond a week are much more likely to be due to atrial flutter than to atrial paroxysmal tachycardia.

Sinus tachycardia differs from paroxysmal tachycardia in that it does not start or stop suddenly; the heart rate accelerates gradually, e.g., from 80 to 100, 120, 140 per minute and similarly subsides gradually instead of in a few beats as do the paroxysmal tachycardias. Furthermore, the cardiac rate in sinus tachycardia varies from minute to minute, especially with change in posture and exercise and occasionally with respiration. The heart rate in paroxysmal tachycardia persists with almost mathematical constancy (allowing a maximal variation of 2 beats per minute for difficulty in counting) despite posture, exercise or respiration. Atrial flutter may disclose equal constancy in cardiac rate, but occasionally there are sharp arithmetical divisions in rate due to heart block, e.g., the rate may be reduced to one-half its previous rate. With exercise, the ventricular rate in atrial flutter may increase in some arithmetical ratio, e.g., from 150 to 200 due to a change from 3:1 to 2:1 block, whereas the increase in rate following exercise is much more gradually progressive in cases of sinus tachycardia.

Carotid sinus pressure[171] may be of value in differential diagnosis as well as in treatment. *Sinus tachycardia* may not alter or it may respond with slight gradual slowing followed by a rapid return to the previous rate. *Atrial paroxysmal tachycardia* is usually suddenly reverted to normal sinus rhythm after a very brief pause or a few ventricular extrasystoles but often there is no effect. *Ventricular tachycardia* is not modified at all. *Atrial flutter* may be slightly and temporarily slowed or there may be a sharp reduction in rate due to increased atrial rate with induced heart block, but sinus rhythm is not restored as it is in atrial tachycardia. Slowing of the heart rate by carotid sinus pressure may also be useful when combined with electrocardiography using a lead from the third interspace to the right of the sternum. This slowing may reveal P waves previously obscured in T or QRS complexes and thus demonstrate atrial flutter with 2:1 block, independent atrial rhythm in paroxysmal ventricular tachycardia or an A-V nodal rhythm which was confused with atrial fibrillation or complete heart block.

Inspection of the cervical veins is more helpful in differential diagnosis.[180] Sinus tachycardia is associated with the normal "a," "c," "v" waves and the characteristic systolic collapse. In cases of atrial tachycardia the cervical veins may be prominent but not distinctive. On the other hand, ventricular tachycardia may be distinguished by the greater frequency of the heart rate as compared with the prominent jugular "a" pulsations (cannon "a" waves) due to retrograde A-V block. Atrial flutter may be diagnosed by the presence of characteristic rapid flutter "a" waves which are usually more frequent (2:1) than the heart rate.

The *heart sounds* may help to distinguish ventricular tachycardia, for there is sometimes a recurrent variation in the quality or intensity of the first sounds but not in atrial tachycardia. Furthermore, although the rate is persistently regular as in atrial tachycardia, the regularity may not be as mathematically constant in ventricular tachycardia. When listening for several minutes one may discover slight disturbances in the regularity of the heart beat. In atrial flutter, audible atrial contractions may be of differential diagnostic value. When bundle branch block accompanies supraventricular tachycardias, there is a wide splitting of the first sound.[180] In ventricular tachycardia wide splitting of the first and second sounds is the rule. If the heart sounds are single in the case of a rapid,

regular tachycardia, the diagnosis is supraventricular tachycardia

Irregular Tachycardias

If the tachycardia is irregular the arrhythmia is usually atrial fibrillation if the heart rate exceeds 130 per minute Below this rate the irregular rhythm may be due to numerous premature beats with sinus tachycardia Atrial flutter is occasionally irregular when there are dropped beats due to heart block or variations in the degree of block The rate may then be rapid or slow Paroxysmal atrial tachycardia due to digitalis toxicity may be irregular because of varying atrioventricular block Irregular tachycardia may be due occasionally to atrioventricular dissociation with interference or to ventricular tachycardia with interference Differentiation of the various irregular tachycardias is aided by artificial increase of the heart rate to 140 or more with exercise amyl nitrite or atropine This accentuates the irregularity if due to atrial fibrillation while that due to premature beats disappears The same procedure may be useful when there is uncertainty as to the presence of atrial fibrillation with normal or slow ventricular rates due to seeming regularity of the pulse It also differentiates this slow ventricular type of atrial fibrillation from cardiac irregularity due to sinus arrhythmia However exercise will not induce an irregularity when atrial fibrillation is associated with complete heart block and the ventricles are really beating regularly with their idioventricular rhythm or when the a v node becomes the pacemaker of the ventricles (a v dissociation) due to digitalis intoxication

Finally differentiation depends on and is made most certainly by a study of electrocardiograms the findings in which are discussed in detail under the individual headings Esophageal electrocardiograms and leads from the right side of the precordium are helpful when it is desirable to depict the P waves most clearly e g when conventional electrocardiograms fail to distinguish ventricular tachycardia from supraventricular tachycardia with bundle branch block

It is worthy of note that oppression of the chest or severe pain may so dominate the clinical picture of a paroxysmal tachycardia that it is mistaken for an acute myocardial infarction Occasionally this difficulty is enhanced by the association with the pain of weakness fall in blood pressure and pulse pressure and rarely of mild fever and leukocytosis However a careful history discloses that the onset was dominated by the tachycardia and palpitation and that the intense thoracic oppression or pain and the circulatory disturbances occurred secondarily Conversely paroxysmal tachycardias may develop after an acute coronary occlusion but they appear days after the basic clinical manifestations of acute myocardial infarction Sometimes the circulatory disturbances incidental to a severe and prolonged paroxysm of atrial tachycardia may induce myocardial infarction in patients with severe coronary atherosclerosis and deficient coronary reserve

From the diagnostic viewpoint it is appropriate to recall that the observation of paroxysmal atrial fibrillation should suggest a search for hyperthyroidism or less likely for mediastinal disease In cases of established atrial fibrillation without apparent cause one should consider the possibility of having overlooked an underlying mitral stenosis or masked hyperthyroidism

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Chapter 15

DISTURBANCES IN CONDUCTION HEART BLOCK AND BUNDLE BRANCH BLOCK

The disturbances in conduction known as heart block may be classified as

1. Sinoatrial block
2. Atrioventricular block
3. Bundle branch block including intraventricular block
4. Short P R interval with prolonged QRS complex

SINOATRIAL BLOCK

Sinoatrial block is a disturbance in which the atrial response is delayed or omitted because of partial or complete interference with the propagation of impulses from the sinoatrial node to the atria [1,4] Experimentally such block has been produced and demonstrated by isolating the s a node through ligation and recording simultaneously the activity of the s a node and other parts of the atria [24] Despite regular sinus impulse formation there is no response of either atria or ventricles because the impulse cannot reach these structures In clinical experience such sinoatrial block cannot be distinguished from sinus arrest or sinoatrial standstill (p 325) in which there is a failure of sinus impulse formation

Electrocardiographically sinoatrial block is characterized by a pause during which a P wave and its accompanying QRST complex are lost (Fig 85) The P P interval is twice or almost twice the dominant P P interval Occasionally the block persists over two three or more cycles and the P P pause is correspondingly prolonged The pauses may not be exact multiples of a normal P P interval because as in all disturbances of the sinoatrial node there may be an associated sinus arrhythmia and because the sinoatrial conduction time may vary from beat to beat just as the a v conduction may vary in a v heart block

There may be recurrent sinoatrial block in which there is an interruption of alternate sinus impulses (2 1 sinoatrial block) The atrial rate becomes halved e g from 76 to 38 per minute and secondarily of course the ventricular rate is likewise halved This simulates sinus bradycardia electrocardiographically and atrioventricular heart block clinically If the sinoatrial block leads to a complete absence of atrial response the condition is termed atrial standstill (p 325) In this condition atrial contractions disappear for a long or short period while the ventricle responds to impulses from a lower center An analogy is sometimes made with atrioventricular block viz (1) isolated atrial pauses (partial sinoatrial block) corresponding to partial a v block with dropped beats (2) recurrent atrial pauses every second beat or third beat etc (high grade but incomplete 2 1 3 1 sinoatrial block) corresponding to incomplete 2 1 3 1 etc a v block and (3) atrial standstill with ventricular response to a v node or idioventricular center (complete sinoatrial block) corresponding to complete a v block with idioventricular rhythm Occasionally prolonged atrial standstill develops without the appearance of an a v nodal or other idioventricular pacemaker in consequence Adams Stokes attacks may occur because of prolonged ventricular standstill As a rule however after the dropping of a few beats an a v nodal beat escapes or with more complete sinoatrial block a v rhythm develops Electrocardiograms of sinoatrial block may have a bizarre appearance due to the intrusion of escape (a v nodal) beats and the appearance of unconducted normal atrial contractions (P waves without following QRS) due to their precocious development after the escape beat and while the ventricle is still refractory (See interference dissociation p 330)

There is a frequent association of a v block

with sinoatrial block. The former may be denoted by prolonged and varying P-R intervals or there may be complete heart block (p. 386). The sinoatrial block may appear occasionally in a case of permanent complete heart block,[a] or sinoatrial block may lead to almost complete atrioventricular dissociation without primary a-v block.[11]

Etiology

Sinoatrial block usually results from sensitivity to or intoxication by digitalis, quinidine, or Neo-synephrine or is associated with hyperkalemia. It may also be caused by vagal stimulation due to a sensitive carotid sinus, tumors compressing the carotid sinus, vagal reflexes during anesthesia and surgical procedures, or because of cerebral lesions. The reported occurrence of sinoatrial block with deep inspiration and its disappearance after the administration of atropine also support the causal importance of vagal influence.

According to Kisch and Zucker[15] sinoatrial block is never a physiologic phenomenon but is due to several factors acting together, e.g., myofibrosis in the region of the s-a node, increased vagal tone and coronary insufficiency. Sinoatrial block may be observed in the course of acute infections such as diphtheria, pertussis or mumps. *It is also possible that* sinoatrial block is due rarely to organic lesions in the neighborhood of the sinoatrial node, e.g., following atrial infarction.

Clinical Aspects

Sinoatrial block occurs much more rarely than atrioventricular block. It is usually of no clinical importance, but with long or frequent pauses in the heart beat the patient may experience dizziness, faintness or even attacks of the Adams-Stokes syndrome (p. 390). Death may occur when there is prolonged cardiac standstill.

Differential Diagnosis

Sinoatrial block may have to be distinguished from sinus bradycardia and from atrioventricular block. The electrocardiogram is usually distinctive. Clinically, atrioventricular block may be distinguished from sinoatrial block by the finding of atrial "a" waves in the cervical veins during the pauses in heart sounds in the former. Atrial "a" waves are absent in the pauses due to sinoatrial block.

Treatment

Treatment is rarely necessary since there are usually no symptoms. When sinoatrial block is due to digitalis or quinidine, these drugs should be stopped. If attacks of dizziness or syncope occur, atropine, 0.6 mg. to 1.0 mg. (1/100 to 1/60 grain), may be given subcutaneously and repeated after two to four hours as needed and tolerated. Ephedrine, 25 mg. (3/8 grain), every four to eight hours as tolerated, may also be useful. For attacks of syncope or Adams-Stokes syndrome, epinephrine may be given parenterally (0.3 to 1.0 cc. of 1:1000 solution) or isopropyl arterenol (Isuprel) 5 to 15 mg. may be administered sublingually at regular intervals as required to prevent the attacks (p. 393).



Fig. 85. Sinoatrial block in woman aged 57 with diabetes and coronary artery disease. Pauses approximately equal to two normal intervals in long strips. After the first pause there is a nodal beat.

ATRIOVENTRICULAR BLOCK

Atrioventricular block is the cardiac mechanism resulting from defective conduction of the impulse from atrium to ventricle. There may be merely a delay in transmission of the impulse through the a-v node and bundle, or there may be a complete interruption of occasional or of all impulses. Accordingly, atrioventricular block is classified as:

1. Prolonged atrioventricular conduction time (first degree block)
2. Partial heart block (second degree block)
3. Complete heart block (third degree block)

Heart block may be transient or permanent and it may represent a functional or organic disturbance. Complete heart block may appear in recurrent attacks with normal conduction between attacks.[17] Heart block is one of the commoner disorders of the heart beat. Its incidence is uncertain because the lesser degrees of heart block are mostly overlooked

However it is probable that heart block is exceeded in frequency only by premature beats atrial fibrillation and paroxysmal atrial tachycardia Prolonged a v conduction time partial heart block and complete heart block are encountered in that order of frequency

Mechanism

Experimentally atrioventricular block can be produced by cutting ligating clamping or otherwise injuring the a v bundle (of His) [3] Ligation or artificial embolization of the coronary arteries the application of destructive chemicals or cold drugs such as morphine epinephrine or digitalis diphtheria toxin asphyxia [28] and vagal stimulation (especially of the left vagus[29]) have been employed to cause heart block experimentally The toxic agents produce heart block either by direct action on the conduction tissue or indirectly through vagal stimulation or both It has been shown that the most susceptible site i e the site responsible for the block is the upper portion of the atrioventricular node

If the bundle is only partially divided with varying degrees of completeness or if progressive degrees of compression are applied various stages of heart block are induced (1) The sinoatrial impulses may all traverse the a v node and bundle and cause a ventricular response but the delay in conductivity results in a prolonged atrioventricular (or P R) interval (2) Occasional sinus impulses cause atrial contractions but are not followed by a ventricular response (3) There is a regular sequence of dropped beats with an atrioventricular ratio of 8 7 5 4 or 4 3 etc Or the ventricle responds to every second third or fourth atrial contraction resulting in 2 1 3 1 or 4 1 block (4) Finally with complete block none of the atrial impulses reaches the ventricles However the ventricles continue to beat independently of the atria (a v dissociation) in response to a pacemaker in the a v bundle below the site of block or rarely in response to a pacemaker in the ventricular musculature (idioventricular rhythm) If at the onset of complete heart block a new pacemaker fails to appear ventricular standstill occurs

The Electrocardiogram

1 *Prolonged Atrioventricular Conduction Time* The P R interval exceeds 0 2 second (Fig 86) It may be as long as 0 3 second and occasionally 0 5 second or more As a rule every P wave is followed by a QRST complex and the waves are normal in configuration In such instances the rhythm of the heart is regular and the prolongation of a v conduction is betrayed only by the electrocardiogram However delayed atrioventricular conduction may be combined with more severe degrees of a v block When the P R interval exceeds 0 3 second there are usually occasional dropped beats which result in some irregularity

Normally the P R interval varies between 0 12 and 0 2 second At slow cardiac rates (60 per minute or less) a P R interval up to 0 21 or 0 22 may be normal P R intervals exceeding 0 2 second and up to 0 28 second were found in 16 of 1000 young apparently healthy aviators [30] A follow up study after ten years showed that none of the individuals with a prolonged P R interval had developed clinical evidence of heart disease [31] When the prolonged P R interval is due entirely to widening of the P wave there is no impaired conduction through the a v node and bundle With very long P R intervals or with rapid rates the P R interval may be difficult to measure because the P wave becomes obscured by the preceding T or QRS complex The presence of a very high or deformed T wave often suggests fusion with the following P wave

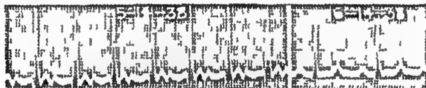


Fig 86 Atrioventricular block in rheumatic fever Lead II May 14 P R interval prolonged to 0 28 during rheumatic activity June 14 ventricular rate slowed but P R interval still prolonged

2 *Partial Heart Block (Second Degree Block)* There are various grades of partial heart block according to the frequency with which atrial impulses are not followed by ventricular contractions

(a) Periodically there is a dropped beat For example, there may be seven P waves followed regularly by QRST complexes while the eighth P wave has no subsequent ventricular complex If the ninth P wave and corresponding ventricular complex follow at their regular interval the mechanism would be termed an 8 7 block denoting 7 ventricular responses to 8 atrial beats The contours of the various waves are unaltered

(b) Occasionally the P-R interval increases progressively until a QRS complex falls out Following this the P R interval becomes smaller but thereafter again increases progressively until there is another dropped beat and seriatim This has been termed the Wenckebach phenomenon and the increasing intervals between beats are called Wenckebach periods (Fig 87) It is believed that the

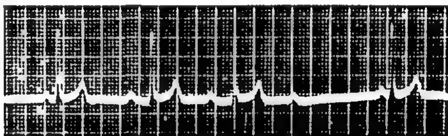


Fig 87 Atrioventricular block with Wenckebach periods Lead II Progressive prolongation of P R interval until after fourth P wave a beat is blocked P R interval after pause is shortened.

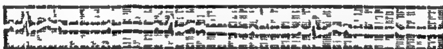


Fig 88 Incomplete heart block 3 1 Lead II There is a ventricular response to every third sinus impulse and the P R interval is constant

progressive delay in conduction denotes increasing fatigue of the a v node or bundle until it is incapable of conducting an impulse at all With the rest period occasioned by the dropped beat, the bundle recovers partially, the P R interval is somewhat shorter but again with each conducted impulse the speed of conduction becomes impaired In this type of partial heart block the ventricular rhythm is irregular, partly because of the changing P R interval and partly because of the dropped beats

(c) With more severe partial heart block the ventricles respond only to every second, third or fourth beat resulting in 2 1, 3 1 or 4 1 block (Fig 88) This is indicated by QRST complexes following every second, third or fourth P wave, but not the intermediate P waves The ventricular rate is usually regular and may be slow if the atrial rate is normal However, the ventricular rate may be rapid e g , 150 per minute in cases of atrial flutter with atrial rates of 300 per minute and a 2 1 heart block At times there is a dominant degree of block e g 3 1 with variations from 2 1 to 4 1[29] In such cases there may be an irregularity in the ventricular rate *High grade block* denotes almost complete heart block with only occasional sinus impulses eliciting a ventricular response (Fig 89)

3 **Complete Heart Block** The essential electrocardiographic feature of complete heart block is the virtual regularity of atrial and ventricular activity with continual variation in the P R interval (Fig 90) The atrial rate is higher than the ventricular rate, i e , there are more P waves than QRS complexes But both the atrial and the ventricular rhythms are essentially regular As a rule the atrial rate is 70 to 80 per minute (normal), while the ventricular rate is 30 to 40 or half as great This simulates but should not be confused with 2 1 block, for in 2 1 partial heart block the QRS complexes follow every second P wave after a constant interval There may be not only complete atrioventricular block but also a 2 1 idioventricular block, i e , the idioventricular impulse may be blocked and the ventricular rate may be less than 15 per minute (double a v block)[14]

The QRS complexes bear no constant time

relationship to the P waves Measurement of the P R intervals discloses irregular variations The QRST complex represents a response to a pacemaker in the a v junctional tissue or in the ventricles while the P wave denotes excitation by the sinoatrial node There is, therefore an atrioventricular dissociation in complete heart block The occurrence of interference with dissociation has been described (p 330) Occasionally P waves recur regularly while there is an abnormally long period without QRS complexes (ventricular asystole) (Fig 91)

block Occasionally complete heart block results from bilateral bundle branch block (p 395) The electrocardiogram is then characterized by atrioventricular dissociation with bizarre QRS complexes like those of ventricular premature beats or bundle branch block (p 335) A distinctive feature in these cases is the tendency for the QRS complex to shift in configuration from the right to the left or from the left to the right type of ventricular premature beat or bundle branch block[44] Ide[44] noted the QRS complexes of left bundle branch block in 18 and of right

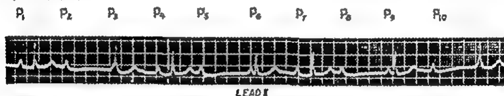


Fig 89 Heart block of very high grade with irregular ventricular rhythm Atrial rate 78 per minute Atrial rhythm almost regular but the P P intervals including the QRS-T are slightly shorter (0 70 sec) than the others (0 84 sec) P_1 P_4 and P_7 elicit a ventricular response Other QRS complexes represent independent (escaped) nodal rhythm



Fig 90 Complete atrioventricular heart block during acute myocardial infarction Ventricular rate 35 Atrial rate 130 Constantly changing relationship between P and R



Fig 91 Complete atrioventricular block with prolonged ventricular asystole

The QRS complexes in complete heart block[44] *are usually of normal configuration* although slight distinctive modifications are observed intermittently when a simultaneous P wave is incorporated in the QRS The normal supraventricular configuration of the QRS complex denotes that the governing impulse arises in a center within the bundle of His or a v node below the site of obstruction and that its subsequent course through the bundle branches and ventricular musculature is normal If however the pacemaker for the ventricles arises in an ectopic focus in the ventricular musculature or in one of the bundle branches the QRS complexes appear widened slurred or notched (aberrant QRS) But similar aberrant complexes may be due to bundle branch block associated with atrioventricular

bundle branch block in 8 instances in a total of *71 cases of complete heart block In 11 of* these the bundle branch block was noted at times when the complete heart block was absent

Although the P waves in cases of complete heart block are usually normal in configuration rate and rhythm they may be absent or replaced by 'f' waves when atrial fibrillation is associated In Ide's series of 71 cases of complete heart block atrial fibrillation was associated in 20 Atrial flutter may also be associated with complete heart block[44] [n] The rate of the P waves may also be accelerated if heart block is combined with atrial flutter or tachycardia

The P waves may not recur with absolute regularity for both in partial [illegible] and com-

plete heart block the P P periods in which a QRS complex falls may be slightly briefer than the other P-P intervals This indicates that the atrial impulse may in some way be influenced by a preceding ventricular contraction,[98] perhaps through modification of vagal tone [illegible] Sometimes more severe types of irregular sinus rhythm occur in heart block the mechanism for which has been variously explained [illegible] [11] The P waves following a QRS may appear to be premature but are usually distinguishable from an atrial extrasystole because in the latter the configuration of the P wave is altered as well as premature Occasionally this distinction fails because the shape of a P wave in cases of heart block may be abnormal if it occurs early in diastole

Sometimes there is retrograde conduction from the ventricular pacemaker to the atrium despite the complete heart block This depends on the time relationship of the idioventricular beat to the preceding normal atrial contraction In order to produce an atrial response the ventricular impulse must arrive when the atrial musculature is no longer refractory

Following stimulation of nerve or muscle there is a period of *complete refractoriness* to further stimulation followed by a *relatively refractory* period when these tissues respond only to stronger stimuli than are usually effective Under certain circumstances, during the recovery period following stimulation there is a brief stage when the muscle may respond to weaker stimuli than usual (i e subthreshold stimuli) This is known as a *supernormal recovery phase* and is observed occasionally in cases of heart block, early in diastole [illegible] Thus P waves occurring early in diastole may be conducted while those occurring late in diastole are blocked The supernormal phase of conduction has also been related to the occurrence of premature beats at this stage of the cardiac cycle

Etiology and Pathology

The commonest clinical causes of heart block (including all degrees of severity) are

1 Chronic forms of heart disease especially severe coronary heart disease, calcific aortic stenosis (usually rheumatic) and less often other forms of rheumatic heart disease, congenital heart disease syphilitic heart disease, syphilitic gumma and gummatous myocarditis, and neoplasms

2 Digitalis in full doses and, less commonly quinidine

3 Acute infectious diseases, notably rheumatic fever and diphtheria but at times almost every other infection

4 The tachycardias Atrial extrasystoles

In Ide s[39] series of 71 cases of complete heart block coronary and hypertensive heart disease was present in 41, digitalis intoxication in 12, and in 9 others the heart block was regarded as congenital As a rule the causative factors under the last three headings induce only a functional and transient heart block,[40] while the chronic forms of heart disease, being associated with anatomic lesions, give rise to heart block which is usually but not always permanent In many instances in which *functional disturbances* are responsible for precipitating heart block there is also organic heart disease which acts as a predisposing or contributory factor

Various forms of *reflex vagal stimulation* may account for transient heart block, characterized usually by a prolonged atrioventricular conduction time but occasionally by complete a v dissociation Heart block may result from compression of the carotid sinus or pressure over the eyeball through the intermediation of vagal reflexes Mackenzie[70] had already noted that swallowing which reflexly stimulates the vagus produced a failure of ventricular response in a patient who previously exhibited only a prolonged atrioventricular interval Similarly Weiss and Ferris[1 8] described the occurrence of Adams Stokes attacks with transient complete heart block due to a vagovagal reflex provoked by a traction diverticulum of the esophagus In at least two of the cases of heart block reported by Holmes and Weill [33] in which heart block was present when the subjects were in the supine position and abolished by standing vagal influence was demonstrated

The heart block caused by *digitalis* may likewise be due to the vagal action of the drug for it is sometimes abolished by full doses of atropine However, the heart block is more often caused by a direct inhibitory effect of the digitalis on the a v node and bundle [19] While digitalis may induce heart block of all degrees even in normal subjects the effect is more readily produced when there is already an underlying conduction disturbance The a v block associated with sinoatrial block and a v rhythm has been noted (pp 383, 328)

usually these combinations result from digitalis or vagal stimulation or both

In *rheumatic fever* prolongation of the P R interval occurs commonly and is a valuable diagnostic finding, severer grades of heart block also occur Heart block often of advanced degree is an important and serious complication of *diphtheria* as it denotes a severe diphtheritic myocarditis (p 907) Usually these cases end fatally However Leys[85] reported complete a v dissociation in a woman of 25 years which he believed was caused by an attack of diphtheria at the age of 10 Since heart block is also observed in a vast number of other infections such as pneumonia scarlet fever grippe mumps German measles in which lesions of the conduction system have not been demonstrated and are improbable the heart block may be due in part to a toxic effect on the a v node and bundle Such a toxic influence may also contribute to the heart block of rheumatic fever and diphtheria independently of any local lesions The occurrence of heart block during convalescence from many infectious diseases suggests that vagal influences may be significant

In most instances of heart block associated with acute infections there is only a prolongation of the P R interval In such cases the P R interval may often be shortened to normal by the administration of atropine This suggests a vagal factor in the production of the heart block Even in cases of prolonged P R interval due to organic causes such as coronary atherosclerosis or calcific aortic stenosis atropine may normalize the P R interval

The heart block accompanying many paroxysmal tachycardias such as atrial flutter and fibrillation and occasionally atrial paroxysmal tachycardia is generally believed to result from a functional fatigue and refractoriness of the a v node and bundle consequent to the great frequency of atrial impulses trying to gain admission to the ventricles

Coronary Atherosclerosis is the chief cause of permanent heart block which may be partial or complete However transient heart block also occurs following an acute coronary occlusion Heart block when present is almost always the consequence of an occlusion of the right coronary artery since a branch of this vessel supplies the a v node and bundle in more than 90 per cent of hearts Massive infarction of the septum is apt to be associated with heart block because an extensive septal infarction usually denotes occlusion of both left and right conorary branches

That coronary artery occlusion (or severe narrowing) does not more frequently produce atrioventricular block is explained by two circumstances (1) Left coronary artery occlusion rarely produces heart block because the conduction tissues almost always receive their blood supply from the right coronary (2) Right coronary artery occlusion uncommonly produces heart block because the septal branch to the a v node and bundle comes off very early and the occlusion is usually distal to the origin of this branch As a rule histologic examination discloses necrosis degenerative changes or fibrosis of the a v bundle or of both bundle branches[147] However a v block may result from tissue anoxia due to a deficient blood supply to the a v node and bundle[94]

In instances of *calcific aortic stenosis* which is almost always rheumatic in etiology various degrees of heart block may result from extension of the calcific process from the aortic ring to the junctional conduction tissue in the septum However conduction disturbances in this disease may be due also to anoxia of the bundle caused by functional coronary insufficiency (p 701) Calcific aortic stenosis may resemble coronary arteriosclerosis with respect both to conduction disturbance and to the presence of angina pectoris because of relative deficiency of the coronary circulation Heart block may be due to deposits of calcium in the bundle in association with calcification of the annulus of the mitral valve with or without concomitant calcification of the aortic valve[115]

Syphilis is an uncommon cause of organic and usually permanent heart block The conduction disturbance may be due to a gumma infiltrating the bundle of His or both bundle branches to a gummatous myocarditis extending from the aorta or to coronary insufficiency caused by syphilitic aortitis with narrowing of the coronary ostia

Congenital heart block occurs uncommonly but there are several reports of cases[113, 19, 104, 150] It probably composes 10 to 15 per cent of all cases of complete heart block and one-half of those occurring below the age of fifty[19] It results from a defect in the course or development of the junctional conduction tissues and

may be associated with interventricular septal defects.[10a] Congenital heart block without evidence of a septal defect was found in two siblings, in one of whose parents there was also a Wolff-Parkinson-White syndrome.[131] Detailed histologic studies reported by Yater, Leaman and Cornell[148] disclosed a separation of the a-v node from the bundle of His by the central fibrous body. Other occasional or rare causes of heart block, usually permanent and associated with anatomic lesions, are bacterial endocarditis with extension of the bacterial inflammatory changes to the septum, neoplasms, tuberculosis and cysts invading the conducting tissues and traumatic lesions. Heart block has also been noted with aneurysm of the sinus of Valsalva of congenital or bacterial origin.

Age and Sex. In a study of 64 cases of severe heart block, mostly complete, Campbell[10] found that 46 were in the age range between 50 and 70 and that males predominated in the ratio of 4:1. In Ide's series[22] the peak incidence occurred between 70 and 80 years of age and males predominated in a ratio between 2 and 3:1.

Clinical Features

Subjective symptoms are generally absent since the rhythm is usually regular and the rate is either normal or slow. Bradycardia is much better tolerated than tachycardia as regards both precordial discomfort and circulatory disturbances. When impaired conduction is limited to prolonged conduction time, there are never any symptoms. In fact, heart block is usually discovered accidentally during routine examinations, and first degree heart block (prolonged P-R interval) is a chance discovery in electrocardiographic examinations. On occasion there may be local symptoms consisting of precordial discomfort or palpitation due to relatively long pauses between beats or to the thumping of the strong ventricular contractions following the pause. There may be recurrent sensations "as if the heart stops," accompanied by intense anxiety and other psychogenic symptoms. Weakness, precordial or epigastric pain occurs occasionally.

In most instances of heart block there is no significant circulatory disturbance. The dynamics of the heart in complete heart block has been elucidated by studies with rapid biplane angiocardiography with simultaneous electrocardiography.[illegible] Sometimes in the presence of heart block, with slow ventricular rate, the heart may be compensated at rest but not under the stress of exercise. With partial heart block of lesser severity, the heart rate increases with exercise and excitement. On the other hand, the degree of block may be enhanced by exercise and the ventricular rate may be slowed instead of accelerated. When block is complete, the circulation may become insufficient during exercise because of the failure of the ventricle to compensate by an increased rate. An effective circulation is usually maintained even when the ventricular rate is as slow as 20 to 30 per minute. The deficiency in cardiac rate is compensated by the prolonged diastolic period available for ventricular filling and myocardial recovery; this results in an augmented stroke output. But when the pause between beats is sufficiently long (more than 3 to 5 seconds), the patient may experience dizziness or vertigo, faintness or attacks of syncope. These symptoms are observed, as a rule, in the severer grades of partial heart block or in cases of complete heart block, and in older individuals in whom cerebral atherosclerosis may be a predisposing or contributory factor. A history of syncope or convulsions is not uncommon in the cases of congenital heart block.

Morgagni-Adams-Stokes Syndrome **(Adams-Stokes, Stokes-Adams).** This refers to attacks of syncope with or without convulsive seizures due to prolonged asystole (five to ten seconds or more) (Fig. 91). The patient becomes pale, loses consciousness and is found to be pulseless. In more severe attacks (fifteen seconds or more) the pallor is combined with or replaced by cyanosis, the breathing becomes deep and stertorous and a generalized convulsion develops. There may be an associated *Cheyne-Stokes respiration.*[35] After twenty seconds or longer the twitchings disappear, the pulse returns, normal color is restored and the breathing becomes quiet. Nonfatal paroxysms rarely exceed sixty seconds in duration, but recovery has followed longer periods of asystole lasting five to twenty minutes.

These attacks usually occur when there is a failure of ventricular contraction in the course of complete heart block, or when there is a delay in the establishment of idioventricular rhythm in the transition from normal sinus rhythm to partial or complete heart block,[illegible] or in shifts between incomplete and complete

heart block There may be simultaneous atrial and ventricular standstill[173] Adams Stokes syndrome due to paroxysmal ventricular standstill which could be reproduced by carotid sinus pressure was reported in a patient with right bundle branch block but without heart block between the paroxysms[21] Either nervous influences or progressive coronary insufficiency may explain why the regularly contracting ventricle in complete heart block suddenly stops for more or less prolonged intervals Similar Adams-Stokes seizures occur when asystole is the result of periods of ventricular tachycardia or fibrillation with or without associated complete heart block[109] (p 377) Syncope from cardiac standstill may also occur in the normal heart as a result of vagal reflexes from a sensitive or compressed carotid sinus or in instances or sinoatrial block

Other symptoms and signs observed in cases of heart block are those of the associated causative condition or underlying heart disease Manifestations of angina pectoris or of congestive heart failure are not uncommon

Signs of Heart Block There are no physical signs of prolonged atrioventricular conduction time However when sufficiently prolonged it may tend to produce a gallop rhythm and the first heart sound may be diminished in intensity The gallop rhythm results from segregation of the atrial sound by the long P R interval

With prolonged atrioventricular conduction and occasional dropped beats the heart rhythm is regular while the blocked impulses are denoted by pauses

With severe degrees of partial heart block 2 1 3 1 etc or with complete heart block the cardiac rate is slow (40 per minute or less usually but 50 per minute is common in complete heart block that is congenital rheumatic or due to digitalis) In cases of diphtheritic heart block there is often a terminal ventricular tachycardia and there may be a high idioventricular rate of 80 to 100 The rhythm may appear regular or in partial heart block there may be abrupt transitions in cycle lengths In complete heart block the changing time relationship between atrial and ventricular contraction and the consequent change in position of the a v cusps results in corresponding variations in the intensity of the first heart sound[112] The atrial sound may be heard faintly between the regular heart sounds, or by coincidence or close proximity with them cause accentuation or reduplication of the first or second sound In instances of mitral stenosis associated with complete or 2 1 heart block a murmur may be audible with each atrial beat which falls during ventricular diastole

Not infrequently calcification in the interventricular septum can be demonstrated radiologically in cases of heart block[137] There are also often signs of associated heart disease including those of cardiac enlargement and electrocardiographic evidence of previous myocardial infarction

Diagnosis

The diagnosis of delayed atrioventricular conduction can only be made by the electrocardiographic finding of a prolonged P R interval (or by analysis of jugular venous tracings) Its presence may be suspected from the development of a gallop rhythm or variations in intensity of the first heart sound during or after infectious diseases especially rheumatic fever

When the delayed conduction is associated with dropped beats partial heart block is suspected from the regular rhythm with intermittent pauses This may have to be distinguished from premature beats in which however the pause follows a fast (precocious) beat Sometimes auscultation fails in this differentiation as the weak sound of the atrial beat may be indistinguishable from the weak sound of a premature beat Partial heart block is diagnosed essentially by electrocardiographic examination (p 385)

Severe partial heart block e g 3 2 2 1 or 3 1 block or complete heart block should be considered with slow apical and pulse rates of 25 to 50 per minute Occasionally rates below 15 per minute have been recorded[14] However congenital complete heart block is often overlooked because the ventricular rate is relatively fast 40 to 56 and in diphtheritic heart block it may exceed 80 Congenital heart block has been diagnosed in utero by the fetal electrocardiogram and sound tracings with simultaneous electrocardiogram of the mother[4] The diagnosis was suggested by the slow fetal heart rate Severe partial and complete heart block must be distinguished from each other and from intense sinoatrial bradycardia and from sinoatrial block Atrioventricular block may be distinguished from the others by the findings of more atrial (a)

waves in the jugular veins than apical beats. The atrial waves may be observed during the ventricular pauses determined by simultaneous auscultation of the heart. Attempts to increase the heart rate by exercise, atropine or amyl nitrite may be helpful in that the rate increases most in sinus bradycardia and not at all or very slightly in complete heart block. In partial heart block there may be a slight increase in heart rate or an abrupt slowing due to further impairment in a-v conduction. Carotid sinus pressure may further slow the heart rate when the block is partial or have no effect in the presence of complete heart block. Complete heart block may also be distinguishable from partial heart block by the irregular change in intensity of the first heart sound in the former. From time to time there is a sharp accentuation of the first sound at the apex ("cannon sounds").

The diagnosis of severe heart block may be suspected from the occurrence of Adams-Stokes seizures. Usually a-v block is discoverable in electrocardiograms taken between attacks but rarely heart block occurs only during the attack. Among the diagnostic features confirming the suspicion that the attack is due to heart block are: absence of heart or pulse beat during the attack while the atrial sounds may be heard on auscultation and the atrial "a" waves may be seen in the cervical veins; the relatively longer duration of the attack in heart block than in vagal cardiac standstill. The finding of a very slow pulse after recovery also suggests that the syncope was due to heart block. However the heart rate may be 90 or higher as the patient is recovering especially if he is under the influence of drugs, after several hours the pulse slows again. For electrocardiographic diagnosis of complete heart block, see page 386.

Prognosis

The clinical significance and the prognosis of heart block depend on the causative factor. The average duration of life following discovery of complete heart block was [illegible] 5 years among 34 patients reported by Campbell.[10] But a number of instances of longevity with complete atrioventricular block have been reported.[6, 108] Heart block due to vagal reflexes, to digitalis toxicity or to extreme tachycardia is usually insignificant in itself and transient in duration. The underlying conditions responsible for the vagal reflex, the tachycardia or for the administration of digitalis may however, be serious. They, not the heart block, determine the prognosis.

Similarly, various grades of heart block occurring with infectious diseases are usually self limited in duration (hours, days or a few weeks) and scarcely modify the outlook of the basic disease itself. However the heart block occurring with rheumatic fever, and less often with other infections, may persist although this is exceptional. In diphtheria heart block is often of ominous significance but only because it occurs in intensely toxic cases in which there is a severe myocarditis. However if recovery ensues there is no evidence of chronic diphtheritic heart disease. In general it may be stated that the seriousness attached to heart block is justified only when it is a manifestation of a serious underlying disease or toxic state. Sometimes the observation of heart block first suggests the search for and the discovery of some underlying disease or digitalis intoxication.

Heart block is often associated with heart disease and in such cases the outlook varies according to the type of heart disease and its severity. Congenital heart block in subjects surviving childhood is usually compatible with normal activities (including pregnancy, childbirth and manual work) and with a normal life span.[10, 108] Heart block may be transient during an attack of acute coronary occlusion but often it persists and becomes progressively more complete. Heart block in syphilitic heart disease may diminish following antisyphilitic therapy, possibly due to resorption of a gumma.

The development of the Adams-Stokes syndrome with heart block is often of serious omen. Cases of heart block associated with bundle branch block are said to be associated more frequently with Adams-Stokes syndrome and an unfavorable prognosis than those associated with the normal supraventricular type of QRS complex.[illegible] An attack may occur at the onset of heart block but may never again appear. On the other hand these attacks may appear infrequently at first but shortly occur more and more often and with increasing severity. They often denote severe myocardial disease. Death may occur during one of the attacks due to prolonged ventricular standstill. As a rule death occurs suddenly in patients with heart block and Adams-Stokes syndrome. In other cases of complete heart

block associated with coronary and hypertensive heart disease but without Adams Stokes attacks heart failure is the common cause of death

Treatment of Heart Block and the Adams Stokes Syndrome

Treatment is rarely indicated for the heart block itself as it usually is not responsible for symptoms and clears spontaneously Treatment of the causative factor may result in abolition of the heart block Digitalis quinidine and opiates should be stopped If these are responsible for the heart block it will disappear rapidly If their use is essential the heart block may not recur with smaller doses

Heart block may require more specific treatment when it is associated with symptoms especially dizziness faintness or Adams Stokes seizures Treatment may be necessary for the acute attack or to prevent recurrent attacks Direct thumping of the precordium may restore the heart beat when there is prolonged ventricular standstill As a rule drugs must be employed to control the attacks of Adams Stokes syndrome

Epinephrine hydrochloride and *isopropyl norepinephrine* (Isuprel) are the drugs of choice Epinephrine may be injected subcutaneously or intramuscularly in doses of 0 3 to 1 0 cc (5 to 15 minims) but only when the Adams-Stokes syndrome is due to ventricular standstill When the attacks recur with great frequency e g during an acute attack of myocardial infarction this dose may have to be repeated every two hours for a day or two After the first injection or two epinephrine in oil (1 cc contains 2 mg of epinephrine) may be given intramuscularly for prolonged effect This may be repeated after 12 to 24 hours if necessary However this form of therapy has usually appeared to be less effective than more frequent injections of the aqueous epinephrine The intervals can be prolonged and the drug finally discontinued if the attacks regress or subside With dangerously prolonged ventricular standstill an intracardiac injection of epinephrine may be lifesaving but there is some risk that epinephrine will induce ventricular fibrillation It is important to obtain electrocardiographic tracings to be certain that asystole is due to ventricular standstill and not to ventricular tachycardia fibrillation Epinephrine is useful in the former condition because it increases ventricular irritability On the other hand because of this action it is contraindicated in ventricular fibrillation which it tends to prolong rather than alleviate

Isopropylnorepinephrine (*Isuprel*) represents an important advance in the management of the Adams Stokes syndrome Like epinephrine Isuprel increases the cardiac rate the stroke volume the amplitude of myocardial contraction and the coronary blood flow There is a slight rise in systolic and a similar fall in diastolic blood pressure [74] Isuprel increases myocardial irritability more than epinephrine or other sympathomimetic drugs but whereas epinephrine stimulates both the higher and lower cardiac centers Isuprel acts predominantly on the higher centers (sinus and atrioventricular node) [149] It tends to increase the rate of the pacemaker in atrioventricular block usually relocating the pacemaker in the vicinity of the atrioventricular node [107]

Isuprel shows the least tendency to produce cardiac automaticity i e to induce ventricular fibrillation Aside from this superiority over epinephrine it also possesses the advantages of not causing the tremor blanching of the skin and other nervous symptoms produced by epinephrine and of effectiveness when administered sublingually It may also be administered subcutaneously or intravenously Isuprel has been effective in cases of Adams-Stokes syndrome associated with ventricular tachycardia[107] and ventricular fibrillation [91] as well as those with ventricular standstill

Isuprel available in 5 and 10 mg sublingual tablets may be administered sublingually in doses of 10 to 20 mg or subcutaneously 0 2 mg every one to six hours or as required to prevent attacks Isuprel has been administered as a continuous intravenous infusion containing 1 mg of the drug in 200 cc of 5 per cent glucose in distilled water (5 micrograms per cubic centimeter) with the rate of flow adjusted to 9 to 20 drops per minute [■]

Sodium Lactate The intravenous administration of sodium lactate has been reported to control the Adams-Stokes syndrome due to ventricular asystole as well as episodes of cardiac arrest the slow idioventricular rhythm of complete atrioventricular heart block and the slow ventricular rate of partial atrioventricular block and sinus bradycardia [6] The dose employed ranged from 15 cc of molar sodium lactate administered intravenously in

one minute to 960 cc (molar and half molar solution) in five hours according to the urgency of the situation and the response Calcium gluconate may have to be given to prevent or control tetany due to the induced alkalosis Although the mechanism of action of the sodium lactate is uncertain it was thought to increase cardiac rhythmicity chiefly as a result of alkalosis

Methamphetamine (Desoxyn) Syncopal attacks were controlled in 2 cases of Adams Stokes syndrome following acute myocardial infarction by the repeated injection of 20 to 40 mg of Desoxyn subcutaneously, intramuscularly or intravenously A sterile solution of the drug is available in 1 cc ampules containing 20 mg [15]

Oxygen and *aminophylline* (administered intravenously or by rectal suppository) may be useful adjuncts in the treatment of Adams-Stokes syndrome

Atropine sulfate 1 to 2 mg (1/60 to 1/30 grain) may be administered when heart block is due to vagal influences It is sometimes given in conjunction with epinephrine in attacks of Adams-Stokes syndrome

For more chronic use or to alleviate attacks of moderate frequency in ambulant persons other sympathomimetic drugs may be given orally ephedrine 15 to 30 mg (¼ to ½ grain) three to five times daily, Paredrine, 20 to 60 mg (⅓ to 1 grain) three to five times daily If palpitation or nervous symptoms develop, these drugs should be combined with sedatives None of these has proved as effective or useful as epinephrine or Isuprel Atropine may be combined with ephedrine or Paredrine

Barium chloride has been used in doses of 20 to 60 mg (⅓ to 1 grain) because of its tendency to increase ventricular irritability, but its efficiency is questionable

Digitalis would seem to be contraindicated because of its vagal stimulating effect and its tendency to impair a v conduction by direct action on the a v node and bundle Nevertheless it has on occasion prevented attacks relieved symptoms due to heart block or eliminated the heart block itself when all other measures failed The explanation for this effect of digitalis is uncertain but it may be related to its improvement of myocardial efficiency Of course when there are definite signs of congestive heart failure digitalis should be administered as usual, regardless of the heart block

Thyroid extract and thyroxin have been recommended both for acute attacks of ventricular asystole and to prevent recurring attacks Its value for this purpose is unproven Recurrent attacks of syncope associated with ventricular asystole due to a hypersensitive carotid sinus were abolished by inducing mild hyperthyroidism with large doses of thyroid hormone [88] Corticotropin administration eliminated attacks of syncope associated with cardiac arrest in a case of myocardial infarction presumably by suppressing inflammation and abolishing heart block [33]

Quinidine is contraindicated because of its depressant effect in the junctional tissues It was hoped that quinidine would be effective in cases of Adams-Stokes syndrome due to ventricular tachycardia and fibrillation But it was noted that in patients with complete heart block quinidine tended to produce ventricular tachycardia, other prefibrillatory mechanisms and ventricular fibrillation [109, 14]

Procaine amide (Pronestyl) is likewise contraindicated in the treatment of Stokes-Adams syndrome associated with heart block whether the Adams-Stokes syndrome is due to ventricular standstill or ventricular fibrillation [108] The administration of procaine amide in patients with heart block has been followed by further reduction in the ventricular rate by multifocal ventricular extrasystoles and by paroxysms of ventricular tachycardia or ventricular fibrillation Neither has it been effective in preventing or eliminating runs of ventricular fibrillation associated with heart block [77]

Artificial Cardiac Pacemaker for Ventricular Standstill and Adams Stokes Syndrome Resuscitation from Adams Stokes attacks due to ventricular asystole or a very slow idioventricular rate may be effected by the application of external electric stimulation with an artificial portable cardiac pacemaker [150, 95] This is a modification of existing physiologic stimulators and produces monophasic rounded electrical impulses with an average duration of 2 to 3 milliseconds and with the entire wave form lying above the baseline The pacemaker is attached to the patient by two output wires connected to circular chest electrodes, 3 cm in diameter The negative electrode is usually placed at the point of maximum cardiac impulse the positive electrode symmetrically on the right anterior chest or on the left posterior chest Electrical contact is facilitated by the application of electrode paste

and the electrodes are maintained in place by a rubber strap encircling the chest

The patient is grounded by the negative output wire from the pacemaker Usually the patient is also connected to an electrocardiograph and the patient the artificial pacemaker and the electrocardiograph must have a common ground by wires between the electrocardiograph and the pacemaker and between the pacemaker and an external ground The frequency of stimulation is set between 60 and 90 per minute and the amplitude control increased from zero until cardiac responses are obtained Thereafter effective cardiac stimulation is maintained by amplitudes slightly above the threshold level In the experience of Zoll et al [150] the current with effective stimuli ranged from 75 to 150 milliamperes and the voltage from 45 to 100 volts Rosenbaum and Hansen[93] developed an inexpensive portable cardiac stimulator combining a defibrillator and pacemaker This offers promise of both defibrillation and restoration of cardiac contraction without thoracotomy See also Zoll et al [151] (p 1109)

By means of the artificial pacemaker Zoll et al [150] resuscitated 11 patients from attacks of Adams-Stokes syndrome due to ventricular standstill maintained an adequate circulation during persistent ventricular standstill and prevented the recurrence of irregular ventricular tachycardia Three patients survived for many months following resuscitation from recurrent syncope This suggested that the factors responsible for the syncope may subside if the patient is kept alive during the crucial period This applies to the use of epinephrine and Isuprel as well as the artificial cardiac pacemaker The cardiac pacemaker is unable to stop paroxysms of irregular ventricular tachycardia or ventricular fibrillation but is effective in shortening the ventricular standstill which may follow such paroxysms Because of impracticalities and the risk of fatal ventricular tachycardia fibrillation due to changing mechanisms of syncope the cardiac pacemaker is not recommended for short treatment of individual attacks of Adams-Stokes syndrome Prolonged stimulation after resuscitation is advised and has been carried out in 9 patients for periods of 25 minutes to 108 hours Douglas and Wagner[17] used a cardiac pacemaker continuously for seven days and effected recovery in a 72 year old man with Adams-Stokes syndrome and prolonged periods of ventricular asystole Untoward effects include chest pain, muscular twitch and superficial ulcerations under the chest electrodes

BUNDLE BRANCH BLOCK

Bundle branch block refers to a delay in or obstruction to the conduction of impulses in one of the branches of the bundle of His The obstruction may be complete or incomplete The terms intraventricular conduction defect and intraventricular block have been applied to electrocardiographic patterns believed to represent incomplete bundle branch block or multiple obstructions in the Purkinje fibers The term arborization block [49] formerly employed to denote extensive block in the arborization fibers of Purkinje has generally fallen into disuse Pathologic studies have thus far failed to disclose such distinct correlations between the anatomic findings and the electrocardiographic patterns The differentiation into complete bundle branch block incomplete bundle branch block and intraventricular block is essentially electrocardiographic

Chiefly on the basis of electrocardiographic findings a sharp division has been made into right and left bundle branch block Left bundle branch block has been reported to occur four to six times as often as right bundle branch block but more recent studies suggest that the stated predominance of left bundle branch block has been exaggerated [4] The higher incidence of left bundle branch block is related to the greater frequency of damage to the left ventricle Occasionally a complete block of both branches produces a condition identical with atrioventricular block [117, 96a]

The normal sinus impulse after traversing the a v node and bundle courses simultaneously through both bundle branches and their smaller ramifications In this way the excitation process reaches both ventricular cavities passes from the endocardial to the epicardial layer and activates both ventricles at the same time The QRS complex of the electrocardiogram represents the summation of the excitation process in both ventricles its normal duration is 0 06 to 0 09 second

If there is an obstruction in one of the main bundle branches e g the left the excitation process must travel along the (functionally) intact right branch the left ventricle is activated indirectly by passage of the impulse

from the right bundle branch through the interventricular septum to the arborization branches in the left ventricle The excitatory process travels much more rapidly through the specialized tissues of the conduction system than through the cardiac musculature Therefore about 0 04 to 0 05 second is lost in passage of the impulse to the left ventricle through the septal muscle instead of along the left bundle branch This delay in reaching the left ventricle is disclosed electrocardiographically by prolongation of the QRS complex while the abnormal route taken by the excitatory process is documented by an abnormal configuration of the QRS (aberrant QRS) Bundle branch block was produced experimentally and its electrocardiographic pattern described by Eppinger and Rothberger [2] The above classic description of the mechanism of bundle branch block has been contested by Sodi Pallares et al [113, 82] and by Burchell and associates[9] on the basis of experimental observations in the intact and isolated dog's heart respectively According to these studies the excitatory pathway in the ventricular system is from apex to base the left side being activated before the right and the apical portion of the right before the base

Bundle branch block may also be disclosed in many instances by asynchronism of ventricular contraction as seen by fluoroscopy or electrokymography or by simultaneous phonocardiograms and tracings of the carotid and jugular venous pulses [20, 101] In left bundle branch block there is a relative delay in the carotid pulse in right bundle branch block a relative delay in the v wave of the jugular venous pulse tracing

The Electrocardiogram

The essential features of bundle branch block are the *prolonged QRS interval* (0 12 second or more) the *slurring and notching of the QRS complex* and the delay in onset of the intrinsicoid deflection over the ventricle of which the bundle branch is blocked Thus in left bundle branch block the time between the onset of the QRS and the peak of R or R (intrinsicoid deflection) is prolonged in left precordial leads (0 05 second or more instead of normal up to 0 035 second), in right bundle branch block it is prolonged in right precordial leads (0 03 second or more instead of normal up to 0 02) Because of the abnormal course of the depolarization wave, the QRS may be bizarre, often resembling that of a ventricular premature beat

In left bundle branch block the initial septal activation is from right to left instead of left to right Hence there is no Q wave in left precordial leads as is usual normally Following septal activation the right ventricle and then the left ventricle is activated Except for the brief period when the right ventricle is being activated, right precordial leads are facing the negative side of the activation wave Hence they display a QS configuration or an rS if there is early dominance of right ventricular electromotive forces Left precordial leads show an RR′ configuration the first upright wave denoting septal and the R′ left ventricular activation

In right bundle branch block the septum is activated first from left to right then the left ventricle and finally the right ventricle is activated In right precordial leads there is an rSR complex denoting respectively the septal left ventricular and late right ventricular depolarization In left precordial leads there is an initial downward (q) wave for the left-to-right septal depolarization a tall upright (R) wave denoting right to-left (endocardial to-epicardial) left ventricular activation and a downward (S) wave for the final right ventricular left-to-right activation

This classic explanation of the electrocardiogram in bundle branch block namely that the initial portion of the R wave in precordial leads results from the transmission of septal potentials from the unblocked side through the septum cavity and ventricular wall of the blocked side, has recently been challenged by Kennamer and Prinzmetal[64] on the basis of intramural and intracavity potentials in experimental bundle branch blocks

The P wave and the P-R intervals are usually normal since the pathway of the sinus impulse is normal until it reaches the block in the bundle branch However it is not uncommon for bundle branch block to be associated with atrioventricular heart block and therefore with a prolonged P R interval [10] especially in left bundle branch block Occasionally an intraventricular conduction defect (with wide and notched QRS complexes) accompanies atrial fibrillation Under these circumstances P waves are absent but fibrillation "f" waves may be visible while the

QRS complexes occur at irregular intervals. With very rapid ventricular rates bundle branch block may be indistinguishable from ventricular tachycardia. The diagnosis of bundle branch block must always be made with caution during any paroxysmal tachycardia in which the P waves and P-R intervals are obscured.

Localization of Left and Right Bundle Branch Block. Since the earliest experimental studies of bundle branch block in dogs, the common bundle branch block pattern has been attributed to right bundle branch block and the uncommon form to left bundle branch block.[44] A host of observations have provided convincing and now generally accepted evidence that this nomenclature should be reversed. The confusion probably arose from the differences between the dog and human with regard to the relationship of the cardiac chambers to each other, to the chest wall and to the axis of the body. The position of the dog's heart is essentially vertical while that of the human is more horizontal or oblique.

Fahr[24] and also Mann[71] on theoretical grounds and Oppenheimer and Pardee[79] on the basis of pathologic studies first indicated that the accepted patterns for right and left bundle branch block should be reversed. Then Barker, Macleod and Alexander[2] by electrical stimulation of the right ventricle of the human heart exposed for drainage of a purulent pericarditis demonstrated that the main deflection of the QRS complex was upward in extrasystoles from that chamber. Since in a block of the left bundle branch the excitation process must pass from the right ventricle to the left, electrocardiographic pattern of left bundle branch block in any lead resembles that of a right ventricular extrasystole and of right bundle branch block that of a left ventricular extrasystole. According to the above observations, the common electrocardiographic form of bundle branch block formerly termed right bundle branch block is really due to a block of the left main bundle branch and is characterized by a major upward deflection in lead I.

By the use of unipolar precordial leads it became possible in doubtful instances to determine the presence or absence as well as the location of the bundle branch block.[116] Since activation of the myocardium underlying a precordial lead is denoted by a negative (intrinsic) deflection, this negative (S or QS) wave will be delayed if the electrode is placed on the side of the block. In left bundle branch block the descending limb of a broad R (i.e. the intrinsic negative) deflection is delayed in leads V_5 or V_6 while the negative deflection Q or QS occurs early in lead V_1 or V_2 over the right side of the precordium.

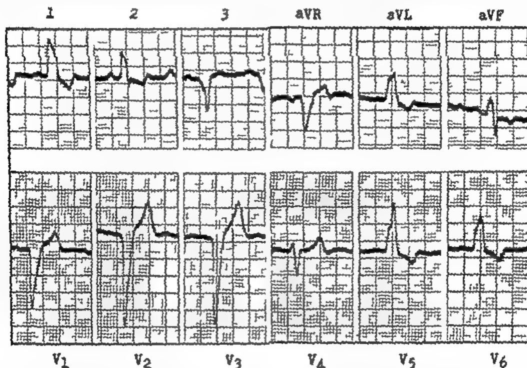


Fig. 92. Left bundle branch block in rheumatic mitral and aortic valvular disease.

Left Bundle Branch Block

The *typical pattern* in standard leads is *characterized by (Fig. 92)*:

1. QRS intervals of 0.12 second or more.
2. Conspicuous notching or slurring of the QRS complexes.
3. QRS complexes of discordant type with the major initial deflection (R) upward in

lead I and the major initial deflection downward in lead III There is no conspicuous [illegible] wave in lead I A Q wave seldom occurs in lead I[114] When it does it may be due to previous septal infarction to peri infarction block[29] to altered cardiac position during respiration or to other factors[44, 111]

4 Large T waves which are opposite in direction to the major ventricular deflections i e T is inverted in lead I and upright in lead III The S T interval is usually depressed in lead I and aV_L elevated in aV_F and lead III

However the electrocardiographic pattern of left bundle branch block may vary from this typical pattern but only as regards items (3) and (4) above Such variations are termed atypical bundle branch block The fact that we are dealing with left and not right bundle branch block is determined from precordial leads As a rule widening (0 12 plus second) and notching of the QRS complex with the major initial ventricular deflection upward in lead I denotes left bundle branch block (unless there [illegible] a broad S wave) The major initial deflection may also be upward in lead III (concordant curves) and the T waves may be deflected in the same instead of in the opposite direction to the main initial deflection in either lead I or III The reasons for these variations from the typical pattern and even for resemblances to the pattern of right bundle branch block are the presence of enlargement of one or both of the chambers of the heart the location and extent of associated myocardial damage and especially the position of the heart in the chest Discordant curves usually occur with normal or transversely placed hearts and concordant curves with vertically placed hearts In vertically placed hearts the pattern in the standard leads may tend to cause a left bundle branch block to resemble a right bundle branch block and a horizontally placed heart may cause right bundle branch block to simulate a block of the left branch[111]

Precordial leads in patients with *left bundle branch block* (Fig 92) are *most important for diagnosis* and are characterized by a delay in the onset of the intrinsic deflection (peak of R wave) in left precordial leads e g , V_5 and V_6 The peak of the R wave does not appear until 0 06 to 0 10 second after the beginning of the R wave instead of the normal of 0 02 to 0 05 second There is often [illegible] notched or M shaped R wave There is no Q wave in V_5 or V_6 because the septum is activated from right to left and the vector is directed *toward* the left precordial lead Over the right precordial leads e g V_1 and V_2 the R wave occurs normally 0 02 to [illegible] 03 second after onset of the QRS or there is an early onset of a deep QS When present the R wave is very small in the right precordial leads There is usually a large T wave

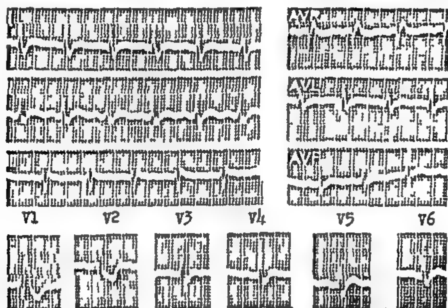


Fig 93 Right bundle branch block [illegible] type Intrinsic deflection (downstroke of R) delayed in V_1 and V_2 [illegible] in V_5 and V_6.

Right Bundle Branch Block

Typical right bundle branch block is characterized electrocardiographically in the standard leads by (Fig 93)

1 QRS complexes 0 12 second or more in duration

2 QRS complexes which are conspicuously notched or slurred

3 *A wide S wave in lead I* which most commonly is of lower voltage than the preceding slender R wave but may exceed the R wave in voltage Rarely there is a wide R wave in lead I

The main deflection in lead III is generally downward in horizontal hearts and upward in vertical hearts When S_1 is not very prominent S_2 and S_3 are

Many variations in the electrocardiographic pattern of right bundle branch block are caused by associated ventricular enlargement myocardial disease or differences in the electrical position of the heart According to the studies of Bayley[4] and of Wilson and his associates[134] there are four or five types of right bundle branch block pattern The commonest pattern of right bundle branch block is that designated as the wide S type or the Wilson block type[135] In this there is a tall slender R wave in lead I followed by a wide S wave of lower voltage and an upright T When this type occurs in a horizontal heart lead III is characterized by a deep Q wave or an rS deflection and an upright T whereas in a vertical heart lead III is characterized by an initial slender upright (R) wave a wide r and an inverted T

A variation of this type of Wilson block includes rare cases in which there is a wide S in lead III as well as in I and II and the wide S may dominate all the standard leads (concordant inverted type)

In the classic but relatively uncommon type of right bundle branch block there is a wide and often slurred S wave in lead I which exceeds the preceding r wave in voltage or there may be no R wave In lead III the main deflection is upward and consists of a slender initial R wave followed by a high positive slurred portion The major deflections in I and III are thus discordant and the T waves in these leads are opposite in direction to the major direction of the QRS (i e upright T_1 downward T_3)

Finally there is a so called unusual type of right bundle branch block[97] in which the R wave in lead I is not slender but as wide as the S wave when the latter is present S_3 is deep and wide and there is left deviation of the electrical axis in consequence this type may be mistaken for left bundle branch block on the basis of the limb leads On the other hand right sided precordial leads disclose late R or R deflections and aV_R shows a qR deflection indicating right bundle branch block However recent vectorcardiographic studies by Richman and Wolff[10] reveal that these cases are actually instances of left bundle branch block with extensive septal and inferolateral infarction

The *precordial leads in right bundle branch block* are of special diagnostic importance The characteristic findings are (Fig 93)

1 R waves which are prominent in leads V_1 V_2 (right side of heart) and which occur late The peak of the R wave occurs 0 04 to 0 10 second or more after the beginning of the QRS instead of the normal of 0 02 to 0 03 second The R wave is broad and notched and often bifid in which circumstance it has been found that the second peak corresponds to the R wave peak in other precordial leads A prominent R wave in right precordial leads occurs not only in right bundle branch block but also in right ventricular hypertrophy without conduction disturbance and in cases of myocardial infarction involving the lateral wall of the left ventricle[1] A prominent Q in these leads suggests septal infarction but a small q may precede a tall slurred and wide R in leads V_1 and V_2 in the uncommon classic type of right bundle branch block

2 Slender R waves which are prominent in leads from the left side of the heart (V_5 V_6) but which occur early The peak of R_5 or R_6 occurs 0 02 to 0 05 second after the beginning of the QRS complex The R wave is usually followed by a broad shallow S The ST segments are usually depressed over the right precordium and elevated over the left precordium The T waves are usually inverted over the right and upright over the left precordium

Incomplete Bundle Branch Block Intraventricular Conduction Defects[7 116]

These terms have been applied to electrocardiographic patterns resembling bundle branch block in which

1 The QRS interval is 0 10 to 0 11 second This is believed to denote some delay in or incomplete obstruction to conduction

through the main bundle branches or their ramifications

2 The QRS complexes are often notched or slurred When present this suggests a deviation from the normal pathway of excitation of one or both of the ventricles

Incomplete Left Bundle Branch Block

When the above pattern resembles that of left bundle branch block i e, the main deflection is upward in lead I downward in lead III with T waves in opposite direction but the QRS interval measures only 0 10 to 0 11 second it may be termed incomplete left bundle branch block The R and S waves are usually of higher voltage than in complete bundle branch block and there is no notching at their peaks

In some electrocardiograms of patients with marked left ventricular enlargement the pattern is that of left axis deviation (p 108) and the QRS interval measures 0 10 to 0 11 second This combination may be indistinguishable from incomplete left bundle branch block The prolonged QRS interval may represent the longer period required to activate the enlarged left ventricle However, precordial leads will not disclose the delay in appearance of the peak of the R wave when the leads are applied over the left side of the heart (V_5 V_6)

Incomplete Right Bundle Branch Block

This is characterized by an rR′ pattern in V_1 and V_E in which the second R wave (R′) is separated from the first by 0 01 to 0 03 second a prominent or widened S wave in left precordial leads (V_6) and a QRS duration of 0 10 in standard and up to 0 11 second in precordial leads [4]

Incomplete bundle branch block may be associated with conditions producing strain or damage to the right ventricle [14] especially congenital heart disease rheumatic mitral disease pulmonary disease with cor pulmonale and coronary disease with ventricular septal infarction [110] Changes in position and conformation of the heart may occasionally produce the above pattern in the absence of delayed intraventricular conduction Differentiation of the electrocardiographic pattern of incomplete right bundle branch block due to right ventricular hypertrophy and that due to defective conduction is facilitated by vectorcardiography (p 118) [55]

The association of right ventricular hypertrophy with incomplete right bundle branch block may be denoted by a very tall R′ wave in V_1 and a very deep S in V_6 And associated left ventricular hypertrophy may be documented by a very tall R in V_6

Vectorcardiogram in Left Bundle Branch Block[33 105] (Fig 91)

Since the ventricular septum is activated from right to left by way of the functioning right bundle and the free right ventricular wall is activated early, the initial QRS vectors are directed downward to the left and somewhat posteriorly These *initial vectors* in addition to close spacing of the time markings of the QRS loop, are the characteristic feature of left bundle branch block and remain constant even in the presence of associated heart disease such as myocardial infarction The initial vectors account for the initial positive deflections in the left precordial leads and in the inferior lead e g V_F and V_E (since the vectors are directed inferiorly and to the left) and for the initial negative deflections in the superior leads aV_R and aV_L and for the initial negative deflections (Q waves) in right precordial leads The time markings are very close, particularly in the middle and distal portions of the QRS loop

In the horizontal projection, the QRS loop is inscribed in a clockwise direction, instead of counterclockwise as occurs normally The long axis of the loop usually lies between minus 30 and minus 60 in the horizontal projection The loop usually fails to close and the ST vector is directed to the right anteriorly and inferiorly resulting in ST elevations in right precordial leads (V_1, V_2) and depressions in aV_L I and left precordial leads V_5 and V_6 The T wave is usually oriented at an angle of approximately 180 degrees to the QRS loop, consequently the T wave is directed opposite to the main deflection of the QRS in the electrocardiogram In some cases the QRS loop in the horizontal projection shows a small initial deflection anteriorly directed resulting in a small positive deflection (r) in right precordial leads In these cases the loop is usually figure of 8 in conformation with the large distal portion inscribed in a clockwise direction

The vectorcardiogram has been helpful in distinguishing left bundle branch block from left ventricular hypertrophy especially in occasional instances of the latter in which the QRS is 0 12 second or longer The vectorcardiogram of left bundle branch block

differs from that of left ventricular hypertrophy in (1) the close spacing of the time markings in the former (2) the inscription of the horizontal QRS loop in left bundle branch block in a clockwise instead of in a counterclockwise direction and (3) the inscription of the *initial part* of the horizontal QRS loop to the left and posteriorly in left bundle branch block to the right and anteriorly in left ventricular hypertrophy

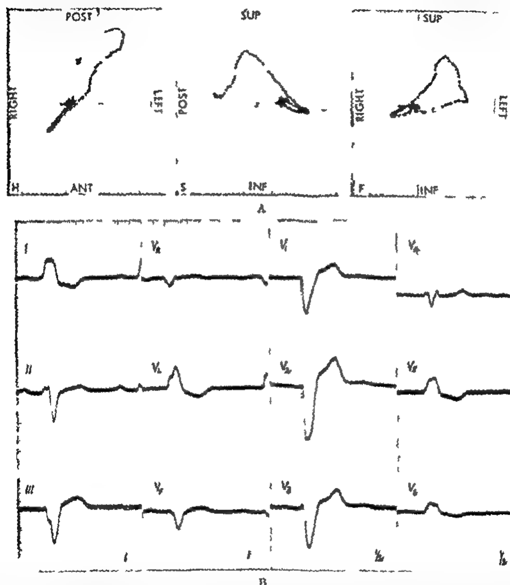
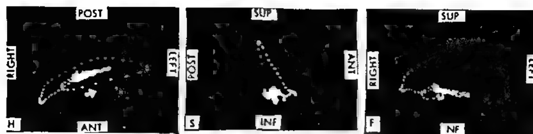


Fig 94 *A* Vectorcardiogram indicating left bundle branch block The vectorcardiogram is inscribed clockwise in the horizontal plane and is directed posteriorly superiorly and to the left Conduction delay is indicated by increased proximity of the time markings in the middle and late portions of the QRS loop H—horizontal S—sagittal F—frontal plane projection

B Electrocardiogram of same patient at speed of 50 mm per second

The Vectorcardiogram in Right Bundle Branch Block (Fig 95)

The Wilson type of right bundle branch block is characterized chiefly by increased duration and slow irregular contour of the *terminal portion* of the QRS spatial vector (SE) loop[54,3] The delay in activation is denoted by *close spacing of the time markings* The terminal portion of the QRS loop forms an appendage directed to the right and an



A

B

Fig 95 *A* Vectorcardiogram indicating right bundle branch block. The initial portion of the QRS is normally inscribed counterclockwise in the horizontal plane projection but terminal portion is irregular slowly inscribed (close time-markings) and forms appendage oriented to the right and anteriorly T loop is directed opposite to this QRS appendage H—horizontal S—sagittal F—frontal plane projection

B Electrocardiogram of same patient.

teriorly whereas the T loop axis is directed opposite to that of the terminal portion of the QRS loop This terminal appendage of the QRS is present even in the presence of associated left ventricular hypertrophy or myocardial infarction In the *classic rare form of right bundle branch block* there is similar close spacing of the time markings, especially of the terminal portion but this may occur throughout the QRS loop The QRS loop is directed to the left downward and anteriorly and is open The latter results in a positive ST vector directed upward posteriorly and to the left which is disclosed electrocardiographically by ST elevations in aV_R and aV_L and left precordial leads and depression in aV_F III and right precordial leads

The *vectorcardiogram* may be useful in the differential diagnosis between left or right incomplete bundle branch block which is due to conduction disturbance and that due to left or right ventricular hypertrophy[11] (p 118)

Recurrent (Paroxysmal) and Intermittent Bundle Branch Block

When bundle branch block appears temporarily but continuously for hours or days we speak of it as paroxysmal bundle branch block Recurrent attacks of bundle branch block have been described repeatedly[103, 111, 84] Such recurrent attacks may be functional in cases of tachycardia without underlying cardiac disease or they may occur in cases of organic heart disease in which a variety of factors impair the conductivity of the conduction system As a rule recurrent bundle branch block occurs in patients with recent or old myocardial infarction or chronic coronary and hypertensive heart disease

Occasionally QRS complexes denoting bundle branch block alternate with normal QRS complexes or they may appear more or less regularly in ratios of 1 1 1 2 or 3 2 block etc the first figure representing the number of normal complexes and the second the corresponding number of block complexes Such curves are termed intermittent bundle branch block They probably result from partial block or defective bundle branch conduction of variable degree Cases of intermittent or unstable bundle branch block have been described in which the presence of the block or of normal conduction depended on whether the ventricular rate exceeded or fell below a critical value[127, 111] The critical rate may be within normal limits or within the range of bradycardia or tachycardia Sometimes there is a progressive change from normal to typical QRS complexes of the branch block variety resembling the Wenckebach phenomenon of partial atrioventricular block with dropped beats Presumably the conduction time through the bundle branch increases gradually until there is a block This permits recovery of the bundle branch and the next impulse passes normally and so on seriatim

Etiology and Pathology

In the great majority of cases of bundle branch block the probable cause is coronary atherosclerosis with recent or old occlusion and associated hypertension The bundle branches may be damaged and blocked by acute infarction and subsequent fibrosis Or a more gradual degenerative and fibrotic alteration may be due to chronic coronary atherosclerosis with myocardial ischemia

Pathologic and electrocardiographic correlations are often uncertain owing to the paucity of studies and especially to technical difficulties Often there is no correlation between the vessels occluded the site of infarction and the type of branch block In some cases of typical bundle branch block as seen in the electrocardiogram serial sections of the atrioventricular conduction system showed no anatomic lesion of the bundle branches[102] Lesions may be found involving both branches[145] especially in extensive septal infarction Right bundle branch block like left bundle branch block may be due to an isolated septal lesion interrupting the single branch[81, 84] Because the right bundle branch receives its blood supply from early perforating branches of the left coronary artery and because of its superficial location below the anterior septal surface the right bundle branch may be blocked in mild anteroseptal infarction However in posterior wall infarction it is not apt to be involved unless there is extensive septal infarction[84]

Left bundle branch block or right bundle branch block may occur in the absence of apparent cardiac disease but this is much more common with right bundle branch block[147] About 25 to 50 per cent of cases of right bundle branch block are unaccompanied by symptoms or signs of organic heart disease but the incidence is less in series of cases observed in a cardiac clinic or observed because of suspected cardiac disease Probably

90 per cent or more of the patients with organic heart disease and left bundle branch block have coronary and hypertensive heart disease or aortic valvular disease especially calcific aortic stenosis

Among cases of right bundle branch block with organic heart disease about 75 per cent are due to coronary and hypertensive heart disease about 15 per cent to rheumatic cardiovalvular disease 3 per cent to acute or chronic cor pulmonale about 3 per cent to congenital heart disease and smaller numbers to other rarer causes When rheumatic mitral stenosis is associated with bundle branch block the pattern is usually that of right bundle branch block [4]

Incomplete right bundle branch block is associated most frequently with congenital heart disease (especially interatrial septal defect or pulmonic stenosis) and with mitral valvular disease but coronary and hypertensive heart disease and chronic cor pulmonale also account for many cases In one-quarter to one-half the cases of incomplete as in complete right bundle branch block, there may be no apparent organic heart disease

Other causes of bundle branch block are syphilitic gumma or luetic aortitis with gummatous myocarditis diphtheria tumors cysts trauma bacterial endocarditis and perhaps other bacterial or viral infections or myasthenia gravis Quinidine procaine amide and digitalis may cause a toxic impairment in bundle branch conduction A toxic bundle branch block may occur in uremia and hyperkalemia [7] Bundle branch block has *occurred as a temporary phenomenon in* thyrotoxicosis [8] Functional disturbance may result from any severe paroxysmal tachycardia and atrial flutter with subsidence as the rate slows and from acute right ventricular strain due to massive pulmonary embolism Four cases of persistent right bundle branch block following pulmonary valvulotomy and infundibular resection were reported [45] There was also a report of 4 cases of benign left bundle branch block in two generations of one family of 13 living members [14]

The *age and sex* of patients with bundle branch block is determined by the cause Since coronary atherosclerosis is the chief cause bundle branch block is observed mostly among males beyond the age of 50

Clinical Features and Diagnosis

There are no symptoms of bundle branch block as such But there may be symptoms of the causative disease Likewise there are usually no specific diagnostic signs Occasionally bundle branch block is associated with paroxysmal or persistent heart block and syncopal attacks of the Adams-Stokes type [120] A palpable reduplicated apical impulse,[47] prolongation or splitting of the first sound and reduplication of the second sound, all due to slightly asynchronous contraction of the ventricles,[131] may suggest the presence of bundle branch block but as a rule the diagnosis is not made on physical examination Bundle branch block is not infrequently associated with a diastolic gallop rhythm and occasionally with pulsus alternans The latter two findings should suggest the possibility that bundle branch block is also present especially if the heart rate is less than 90 per minute

The definite diagnosis of bundle branch block however, depends on electrocardiographic study (p 396) The diagnosis is indicated primarily by the relatively late time of onset of the intrinsicoid deflection as seen in precordial leads and by the prolonged duration of the QRS complexes in standard leads

Course and Prognosis

Bundle branch block occurs transiently or may persist permanently When due to toxic factors which may be removed bundle branch block is a temporary reversible condition Intraventricular block associated with the paroxysmal tachycardia of atrial flutter subsides when the paroxysm ceases The bundle branch block associated with severe coronary atherosclerosis and other forms of organic heart disease is usually persistent but I have several times seen bundle branch block develop at the onset of an acute coronary occlusion and disappear within a few days Bundle branch block may recur intermittently for a period of months and then disappear or become permanent [51] Kalett[43] reported a case of bundle branch block with spontaneous remission after four years and Myre and Fuller[75] after at least three years But as a rule when the branch block persists without remission for several months it is likely to be permanent

Too much importance has been attached to the prognostic significance of bundle branch block It has been stated that the survival

period averaged one to two years although more recently it has been recognized that some patients with this condition survived five to twenty five years or longer [85, 1, 8] Actually the prognosis depends on the underlying cause [112] The unfavorable prognosis usually applied to bundle branch block corresponds to the prognosis of coronary occlusion which is the commonest cause As in recent years we have become aware that the prognosis of coronary occlusion is more optimistic than was formerly thought there has been a correspondingly more favorable outlook for bundle branch block Furthermore bundle branch block occurs more frequently in the younger age right or left ventricular damage and especially in cases of coronary heart disease Papp and Smith[81] recently called attention to the changing electrocardiogram in the Wilson type of right bundle branch block and emphasized that except in rare instances it is a sign of organic heart disease In general it is safer to evaluate the patient and his disease as a whole rather than to base a prognosis on the presence and type of bundle branch block

Treatment

Treatment is directed toward any underlying or associated condition The presence of bundle branch block in itself is no indication for treatment However when it results from

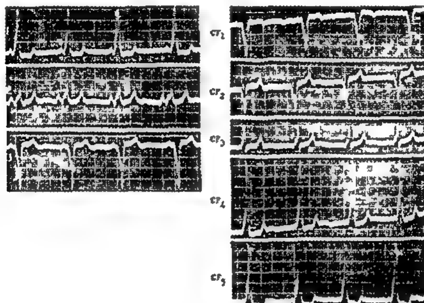


Fig 90 Wolff Parkinson White syndrome Short P R interval with bundle branch type of QRS (0 13 second in lead I)

groups than was formerly believed in these there is no apparent evidence of heart disease and the outlook is benign [85]

Right bundle branch block is considered to offer a more favorable prognosis than left bundle branch block [8, 116] Such generalization must be accepted with caution especially in view of the uncertainties as to the interpretation of patterns now believed to represent right bundle branch block In the series of cases studied by Taimont et al [105] right bundle branch block of the classic or rare type was found only in cases with clinical and anatomic evidence of severe right ventricular involvement whereas the Wilson or S type was equally distributed among cases with digitalis or quinidine or other intoxication the causative agent should be eliminated if possible

SHORT P R INTERVAL WITH WIDE QRS (WOLFF PARKINSON WHITE SYNDROME)

Electrocardiograms resembling those of bundle branch block but with a short P R interval have been repeatedly noted in young and apparently healthy individuals who are subject to attacks of paroxysmal tachycardia Isolated cases were documented by Wilson[133] and others [22] but interest became widespread only after Wolff Parkinson and White[111] in 1930 reported 11 cases and defined the condition as a distinct entity For this reason it is

often termed the Wolff Parkinson White (W-P-W) syndrome [140] In 1940 Hunter et al [38] collected 90 cases from the literature and added 19 of their own

The essential diagnostic feature is a *distinctive electrocardiogram* (Fig 96) in which QRS complex Consequently the interval from the onset of the P wave to the end of the QRS (P-J interval) remains normal QS deflections in leads II, III and right precordial leads, ST deviations and T wave abnormalities may occur The electrokymogram usually shows a

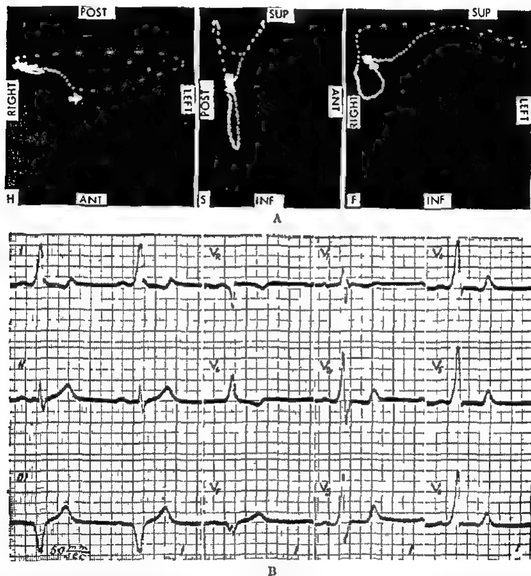


Fig 97 *A* Vectorcardiogram indicating Wolff Parkinson White syndrome in a 16 year old boy with coarctation of the aorta Characterized by very slow (closely spaced) initial segment of QRS loop H—horizontal S—sagittal F—frontal plane projection

B Electrocardiogram of same patient

(1) the P-R interval is abbreviated, measuring 0 10 second or less (2) the QRS complexes are widened (0 11 to 0 14 second) and slurred, (3) there is *slurring* at the onset of the upstroke of the R wave, termed the *delta wave* The shortening of the P-R interval is exactly compensated by the widening of the delay in contraction of both ventricles and occasionally ventricular asynchronism,[100] but this requires further study The *vectorcardiogram* of the Wolff Parkinson White syndrome is characterized by close spacing of the time markings of the initial (centrifugal) portion of the QRS loop[31] (Fig 97)

An essential clinical feature is the tendency to recurrent attacks of paroxysmal atrial tachycardia or atrial flutter Occasionally atrial fibrillation occurs Ventricular tachycardia has also been reported in cases of Wolff Parkinson White syndrome [61 18] but may have represented an instance of atrial flutter with aberrant conduction resembling ventricular tachycardia The Wolff Parkinson White syndrome should be sought in every case of paroxysmal supraventricular tachycardia Jones[41] discovered the Wolff Parkinson White syndrome in 5 of 47 cases of paroxysmal atrial tachycardia and in 4 others there was a probable variant of the syndrome

The characteristic electrocardiographic Wolff Parkinson White pattern is sometimes termed the anomalous mechanism anomalous atrioventricular excitation or preexcitation syndrome This Wolff Parkinson White pattern may be continuous but there is often a spontaneous or induced transformation of the electrocardiogram to a normal P R interval and normal QRS width There may be isolated Wolff Parkinson White beats or Wolff Parkinson White beats alternating with normal complexes There may be progressive widening of the QRS complexes as the P R interval shortens or the widened QRS and narrow P R may gradually return to normal (concertina effect)

The distinctive electrocardiographic features may disappear spontaneously as a result of atropine quinidine procaine amide or amyl nitrite or when the heart rate is increased by exercise In the case reported by Wilson [133] that of a man aged 23 years the electrocardiographic abnormalities appeared after stimulating the carotid sinus or spontaneously When they appeared spontaneously they could be abolished by the administration of atropine Subsequent reports have been conflicting as to the regularity with which the electrocardiographic changes can be eliminated by atropine and exercise Quinidine[92] and large doses of digitalis[104] have been observed to restore a normal electrocardiogram in some cases but in another case digitalis widened the QRS complex [87]

When persons with the Wolff Parkinson White syndrome experience a paroxysm of tachycardia the widened ventricular complexes assume a normal configuration but occasionally they remain aberrant [74] During paroxysms of atrial fibrillation the QRS complexes appear aberrant and may be wider than during periods with sinus rhythm [73] but the absence of P waves during atrial fibrillation prevents a differentiation of wide QRS complexes of the W P W syndrome from those due to true bundle branch block or ventricular extrasystoles The Wolff Parkinson White syndrome may be suspected from the delta wave in the wide QRS complexes The QRS of the W P W syndrome may conceal the Q waves associated with cardiac infarction and it may also obscure the pattern associated with ventricular hypertrophy or right bundle branch block But spontaneous suppression of the Wolff Parkinson White complexes may reveal these changes [14]

Atypical Forms of Wolff Parkinson White Syndrome

A variety of modifications of the Wolff Parkinson White syndrome have been described There may be a short P R interval with normal QRS complexes and episodes of supraventricular tachycardia [87] These were usually observed in middle-aged females devoid of organic heart disease But there has been reported also the occurrence of short P R intervals with normal QRS complexes in coronary thrombosis hyperthyroidism hypertension and in neurotic individuals presumably owing to altered autonomic tone In Oehnell s series of 200 cases with a short P R interval [77] there was a greatly increased incidence of paroxysmal tachycardia whether the QRS was widened as in the Wolff Parkinson White syndrome or of normal width But the incidence of paroxysmal tachycardia was 25 per cent in the former and 10 4 per cent in the cases with a short P R interval and normal width of QRS

In other cases [6] the P R interval may be 0 12 second and the QRS of normal width but the initial portion of the R wave is slurred (delta wave) Other variants have been described by Bordnas et al [7]

Etiology

The Wolff Parkinson White syndrome occurs at all ages but chiefly below the age of 30 and more commonly in males It has been observed with increasing frequency among infants and children [117 21] There is evidence that the mechanism producing the Wolff Parkinson White syndrome may be latent for many years[68] and may be first demonstrated in later life For these reasons and

because the subjects are apparently healthy, aside from the paroxysmal tachycardia, it is deemed probable that the Wolff-Parkinson-White syndrome is of congenital origin. This concept is also supported by reports of the occurrence of the W-P-W syndrome in siblings.[1]

On the other hand, the *electrocardiographic pattern* of the Wolff-Parkinson-White syndrome has been produced in animals by injecting various chemicals or otherwise stimulating the ventricular septum or other parts of the ventricular myocardium[87] and in humans by cardiac catheterization[50, 3] and after intravenous strophanthin.[15] But it is questionable whether these represent an identical mechanism with that of the Wolff-Parkinson-White syndrome.

Mechanism

The mechanism responsible for the W-P-W syndrome is uncertain, although several theories have been offered.[27, 35, 139, 77, 110, 73, 87, 86] Wolff, Parkinson and White[141] attributed the electrocardiographic changes to excessive vagal tone because they could abolish them with atropine or exercise and because occasionally the electrocardiographic abnormalities could be induced by vagal stimulation. This theory was rejected because these effects of atropine or vagal stimulation could not be confirmed in many other cases and because the electrocardiographic changes could not be harmonized with the known effects of vagal stimulation. The various theories attempt to explain the premature activation of a small portion of ventricular musculature (preexcitation) which accounts for the short P-R interval, the delta wave and the wide QRS. The theories propose either (1) anomalous conduction which avoids the delay in passage through the normal a-v node or (2) anomalous impulse formation whereby an irritable septal focus below the atrioventricular node is prematurely excited by electrical or mechanical stimuli from the atrium.[110, 77] The first of these theories has several variants according to the route of anomalous conduction: (a) an accessory muscular or neuromuscular pathway between atria and ventricles[27, 139], (b) along the atrioventricular groove and through the ventricular wall from epicardium to endocardium[2], (c) through a disordered portion of the atrioventricular node which permits accelerated conduction.[87]

The most generally accepted theory is that of Holzmann and Scherf[27] and of Wolferth and Wood[139] who postulated the existence of an anomalous aberrant pathway between the atria and ventricles by which the sinus impulse activated the latter chambers. Wolferth and Wood[139] suggested that this aberrant pathway might be similar to the so-called bundle of Kent, a structure in the heart of the rat, bridging the atrioventricular groove.[46] Subsequently this hypothesis received support by the postmortem discovery of such an accessory bundle in the heart of a child who had exhibited this syndrome during life and who died during an attack of paroxysmal tachycardia.[144] (See also Oehnell.[77]) Histologic demonstration of an accessory right lateral conduction bundle was reported also in a case of septal infarction with complete heart block and intermittent anomalous a-v excitation (W-P-W syndrome[40]). (Normally there are no accessory communications outside the conduction system between atria and ventricles.[59]) The theory of an accessory pathway was also supported by the experimental production[9] of a short P-R with wide QRS when the normal conduction system was short circuited by a vacuum tube amplifier analogous to the alleged short circuiting effect of an accessory conduction bundle. By reversing the connections so that amplified ventricular currents stimulated the atria, paroxysms of tachycardia were induced. Although it is usually believed that the aberrant short conduction pathway connects the right atrium and right ventricle, there are cases of W-P-W syndrome in which the left ventricle is activated before the right.[89, 118]

According to the theory of Wolferth and Wood,[139] the short P-R interval is due to the shorter, more direct pathway through the accessory bundle from the atrium to the ventricle while the prolongation of the QRS results from premature activation of one ventricle. The altered configuration of the QRS especially in its early portion is attributed to the abnormal course of the impulse when it first reaches the ventricle. The anomalous pathway is said to predispose to attacks of paroxysmal tachycardia by facilitating retrograde conduction of the impulse (reentry) into the atrium where under favorable circumstances the abnormal rhythm is initiated. Fox and associates[3] offered the hypothesis that supraventricular arrhythmias

result from a block of the aberrant bundle due to a decrease in "vagus substance" An ectopic focus in the supraventricular portion of the aberrant bundle above the block gives rise to impulses which activate the ventricles by way of the normal bundle

Recently Prinzmetal and associates[27] have marshalled experimental and clinical evidence indicating that the Wolff Parkinson White syndrome results from a disturbance in the atrioventricular node In consequence the normal slowing of conduction through the node is impaired and conduction of the impulse is accelerated through the abnormal part of the node rather than through an abnormal bundle The part of the ventricular myocardium stimulated by the accelerated portion of the impulse is activated earlier than the remainder of the ventricular myocardium which is stimulated by the normal slower portion of the impulse According to Prinzmetal the nodal defect sometimes functions as an ectopic focus to give rise to various supraventricular arrhythmias notably atrial tachycardia but also atrial flutter and fibrillation

Clinical Features and Prognosis

There is no distinctive clinical picture except for the occurrence of supraventricular tachycardia in the vast majority The Wolff Parkinson White syndrome is often the basis of the paroxysmal tachycardias in infancy and childhood There may be a split first sound at the apex a systolic murmur and sinus arrhythmia Although the subjects with Wolff Parkinson White syndrome are almost always free of organic heart disease reports of coronary and other heart disease have appeared repeatedly in recent years[25, 119] but these are coincidental The condition is not always benign even in the absence of organic heart disease for deaths have occurred suddenly in the course of an attack of paroxysmal tachycardia[25] Some patients suffer disability because of frequent recurrent attacks of tachycardia and its attendant symptoms The syndrome is not a contraindication to normal activity pregnancy operations and the like

Diagnosis

The diagnosis of Wolff Parkinson White syndrome is made by observing the characteristic electrocardiographic changes (p 406) However it is often overlooked and therefore should be carefully sought in (1) all patients with paroxysmal tachycardia (2) when the electrocardiogram suggests bundle branch block (3) whenever there is slurring of the initial portion of the R wave (4) when the P R interval is 0 10 to 0 12 second or less (5) when there are spontaneous changes in the duration of the P R interval and QRS (6) when there appear to be runs of ventricular tachycardia during paroxysms of atrial fibrillation[140]

The electrocardiographic pattern of the Wolff Parkinson White syndrome is often misinterpreted to denote heart disease especially myocardial infarction bundle branch block or ventricular hypertrophy This will be usually avoided if the P R interval is carefully measured in the three standard leads

Management of Wolff Parkinson White Syndrome

The electrocardiographic pattern of the Wolff Parkinson White syndrome requires no treatment The patient should be reassured The various forms of supraventricular tachycardia should be treated as in other patients without the Wolff Parkinson White syndrome In cases of paroxysmal atrial fibrillation in which digitalis would ordinarily be effective in slowing the ventricular rate this drug is usually ineffective when there are constant runs of aberrant ventricular beats resembling ventricular tachycardia These should be treated with quinidine which tends to suppress the anomalous mechanism and may also eliminate the atrial fibrillation

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PART IV

DISEASES OF THE CORONARY ARTERIES AND CORONARY HEART DISEASE

Chapter 16

CORONARY (ATHEROSCLEROTIC) HEART DISEASE, OTHER DISEASES OF THE CORONARY ARTERIES

Atherosclerosis is by far the commonest lesion of the coronary arteries Sooner or later in varying degree most hearts are thus affected But only in the minority of cases does coronary atherosclerosis evoke significant myocardial lesions or clinical disturbances of the heart For this reason coronary atherosclerosis is an undesirable term when used to express a clinical form of heart disease

To obviate this confusion the term coronary heart disease has been suggested to represent clinical heart disease due to lesions of the coronary arteries But this is satisfactory usage only if it is recognized that the cardiac disease may be due occasionally to other coronary disturbances besides coronary atherosclerosis e g, syphilitic coronary ostial stenosis The term atherosclerotic heart disease may be employed to designate the various clinical cardiac manifestations due to coronary atherosclerosis and its anatomic cardiac sequelae Atherosclerotic heart disease coronary heart disease and coronary atherosclerotic heart disease are terms commonly used interchangeably The degenerative atheromatous sclerotic and calcific alterations of the endocardium and valves should not be classified as or confused with atherosclerotic heart disease They are essentially purely pathologic lesions the nature of which can clearly be indicated by terms which do not include the words heart disease

This chapter encompasses a general survey of the subject of coronary heart disease Angina pectoris coronary thrombosis and myocardial infarction are almost always intrinsic elements of coronary heart disease but they require sufficiently detailed discussions to justify independent chapters which follow This segregation should not obscure their relation to the general heading of coronary heart disease

INCIDENCE OF CORONARY HEART DISEASE

Coronary heart disease is the commonest form of clinical heart disease beyond the age of 40 With the progressive aging of our population cardiovascular disease has become more definitely the dominant cause of death and coronary heart disease the major form of fatal cardiac disease

The most reliable studies of the incidence of coronary heart disease are those concerned with well defined manifestations such as angina pectoris or acute myocardial infarction (Chaps 17-21) Pathologic evidence indicates that coronary atherosclerosis of variable degree increases progressively with age up to the age of 60 in men [4] and 80 in women [1] But clinical manifestations occur only when it leads to extreme narrowing or occlusion of the lumen of a major coronary branch Among young soldiers killed in action in the Korean war with an average age of 22 years 77 3 per cent had gross pathologic evidence of coronary atherosclerosis [44] But only 10 per cent exhibited advanced disease with more than 70 per cent of the lumen of a major vessel occluded The diagnosis of coronary (atherosclerotic) heart disease refers to clinical manifestations and not to the mere presence of atherosclerotic lesions Extensive pathologic lesions may be present but cannot be diagnosed unless they produce overt clinical manifestations

ETIOLOGY OF CORONARY (ATHEROSCLEROTIC) HEART DISEASE

Underlying Cause

Atherosclerosis of the coronary arteries and the consequent disturbances in the blood supply to the myocardium compose the underlying cause of coronary (atherosclerotic) heart disease Unfortunately our understanding of the genesis of atherosclerosis is still in

adequate The theories offered to explain the pathogenesis of atherosclerosis are discussed below

Predisposing and Contributing Causes

Age and Sex Both the pathologic lesions and the clinical forms of coronary heart disease occur predominantly after the age of 40 and with increasing frequency in subsequent decades In a study of 865 cases of coronary artery disease, Peel[165] found that in men the incidence is significant earlier than in women reaches a high peak at 55 to 59 and thereafter falls steeply In women the rise in incidence is slow and steady from the age of 40 to 70 without an ultimate fall However, instances of advanced coronary heart disease are not rare before the age of 40[59, 242] and the incidence of coronary occlusion in young persons appears to be increasing This has been notable in civilian practice[64] as well as in the armed forces[54] Gertler Garn and White[70] found that 100 young persons with proven coronary heart disease were characterized by a 'resolute and intensive personality' a stocky physique a serum cholesterol level above 309 mg per 100 cc, a serum uric acid above 5 4 mg per 100 cc and a high serum cholesterol phospholipid ratio[70]

Coronary heart disease [illegible] much more frequent among males than among females, but this predominance does not prevail among diabetic patients and is less striking in the presence of hypertension and among subjects beyond the age of 60 [illegible] [15] A satisfactory explanation of atherosclerosis should account for this striking difference in incidence between males and females and the equalizing effect of diabetes and hypertension

Hypertension is found in about 50 per cent of men and in about 75 per cent of women with coronary heart disease[15] Conversely there is a high incidence of coronary heart disease in patients with hypertension[4, 55] Induced hypertension increased the severity of experimental atherosclerosis in rabbits[20] dogs[20] and chicks[10] (But the frequency of coronary heart disease in the absence of hypertension indicates that hypertension is only an accessory or aggravating factor in atherosclerosis and not a primary cause (p 428))

Diabetes Coronary heart disease develops with unusual frequency among diabetic patients and at a relatively earlier age than among non diabetics[18, illegible, 3, illegible, 55] A similar relationship has been noted to familial xanthomatosis with hypercholesterolemia (p 425) Essential hyperlipemia is also associated with premature atherosclerosis Myxedema, chronic glomerulonephritis and obesity are some of the other conditions which have been said to predispose to coronary heart disease

Heredity The occurrence of coronary heart disease in several members of a family is a common observation There are insufficient formal studies and statistical data to justify the conclusion that heredity is an important factor in coronary heart disease But Thomas and Cohen[214] found that clinical coronary artery disease was nearly four times as frequent among siblings of persons with coronary disease as among siblings of persons without it

Body Type Studies of body type have suggested that individuals of the so-called mesomorphic type i e with predominant maleness muscularity and compactness' are most apt to develop clinical coronary atherosclerosis as indicated by myocardial infarction before the age of 40[65] and by necropsy studies of the coronary arteries in males under the age of 46[197]

Obesity There is indirect evidence, based chiefly on life insurance[45] and autopsy statistics[59, 230] that obesity predisposes to fatal coronary atherosclerosis According to life insurance data the mortality from coronary heart disease in obese individuals is 40 per cent higher than among standard risks[45] On the other hand Gertler and associates[67] found that obesity alone was no more common among young men with coronary disease than among other men of the same age and social status Faber and Lund[65] found that obesity had no effect on the development of aortic atherosclerosis in the human if the influence of hypertension was taken into account

Smoking Recently indirect evidence has been accumulating that there is a relationship between smoking and coronary heart disease[90] According to Hammond and Horn[88] there was a 56 per cent increase in mortality over the expected rate in regular cigarette smokers and this increase was even more striking with respect to deaths from coronary heart disease

Dietary Geographic and Ethnic Factors are discussed in connection with the pathogenesis of atherosclerosis (p 426) Coronary heart disease is said to be uncommon among the Chinese Japanese Okinawans Bantu tribes

men in South Africa[155] and others Gilbert[71] found no coronary heart disease among the Navajo Indians in Arizona although the disease is common in other persons in the same area

For additional discussion of some of the above etiologic factors in coronary heart disease see the chapters on angina pectoris (p 449) and acute myocardial infarction (p 493)

DEFINITION AND CLASSIFICATION OF ARTERIOSCLEROSIS

The term arteriosclerosis (hardening of the arteries) refers to a variety of degenerative vascular changes which are best defined by a description of the pathologic alterations The changes due to syphilis rheumatic fever specific infectious diseases thromboangiitis obliterans periarteritis nodosa lupus erythematosus among others are not included under arteriosclerosis The latter comprises three groups of lesions

1 *Medial calcification* with or without preceding degeneration or necrosis (Monckeberg s sclerosis[14]) This produces pipestem and beaded peripheral arteries but does not occlude the lumen or produce significant clinical symptoms The process usually involves medium sized muscular arteries such as the femoral artery These hardened arteries often show little or none of the lipoidal deposits and intimal thickening which characterize atherosclerosis

2 *Arteriolosclerosis (productive or hyperplastic arteriopathy)* which is characterized by endothelial hyperplasia thickening and hyalinization of the intima reduplication of the internal elastic lamina and hypertrophy of the media of the arterioles of the kidney and other viscera These lesions are associated usually with hypertension

3 *Atherosclerosis*[175] which affects chiefly the large and medium sized musculoelastic arteries (aorta coronary cerebral peripheral) It is characterized by intimal thickening due to lipoid atheroma fibrosis calcification necrosis and hemorrhage This is the type of arteriosclerosis which involves the coronary arteries and is responsible for coronary (atherosclerotic) heart disease Arteriosclerosis denoting hardening of the artery is a poor term for this form of disease because it is not the hardening but the intimal changes and thickening which lead to narrowing or occlusion Reference should be made also to the superficial yellowish lipoid deposits on the intima of the aorta and coronary arteries which appear commonly in the first decade of life and appear to be reversible in youth but may progress to atherosclerosis later in life Lande and Sperry [119] in a study of aortas from 89 individuals who had died of trauma or alcoholism without other disease found only 3 without macroscopic evidence of atheroma Early aortic atherosclerotic lesions were also found universally in 300 consecutive autopsies of subjects beyond the age of 7 [147]

Hyperplastic Arteriosclerosis This is a term applied by Moschcowitz[161] to vascular lesions characterized by hyperplasia of the intima and internal elastic layer and by hypertrophy of the media independent of atheromatous lesions Under this heading are included the changes seen in arterioles (classified above as arteriolosclerosis) and medium sized arteries and also those in the coronary and cerebral arteries In the latter the atheromatous deposits are regarded as a secondary facultative not primary lesion of arteriosclerosis

PATHOGENESIS OF ATHEROSCLEROSIS

Theories of atherosclerosis are concerned with two general questions viz (1) whether it is an irreversible immutable process of aging or one due to exogenous or endogenous factors which may be controlled and (2) whether the primary disease is an intrinsic abnormality in the vessel wall which then predisposes to secondary lipoid change either locally or by imbibition from the plasma or whether some primary metabolic change which alters the blood results secondarily in vascular lipoidosis and other degenerative changes The latter disagreement stems from uncertainty as to whether the initial lesion consists of degenerative alteration of the intimal collagen or ground substance [18 11] or of lipid containing foam cells arising in connection with lipid deposited from the blood stream [1]

AGING THEORY OF ATHEROSCLEROSIS

This theory supposes that atherosclerosis is an inevitable consequence of aging and therefore an irreversible process [151] In a general way the occurrence severity and extent of atherosclerosis including coronary atherosclerosis increase with age [197] On the

other hand coronary and other atherosclerosis is *frequently* minimal in very *old* people[17], in fact the absence of severe atherosclerosis of the coronary and cerebral vessels may be a prerequisite to the attainment of old age I have examined many hearts of subjects beyond the age of 70 who died at a home for the aged and often observed that the aorta and coronary arteries were remarkably free from significant atherosclerotic change

Another objection to the aging theory is the occurrence of advanced coronary atherosclerosis in youth e g in postmortem studies of young German recruits during World War I[113] and in young soldiers during World War II[69, 213, 41] and in the Korean War[44] Pulmonary atherosclerosis appears in young individuals dying of rheumatic mitral stenosis or of congenital cardiovascular abnormalities

Aging fails to explain the sharp difference in incidence and severity of atherosclerosis among men and women the reported difference in incidence in different countries, the variations in distribution among the different arteries and the high incidence in association with diabetes, xanthomatosis and myxedema

The atrophic and proliferative changes usually described as characteristic of aging differ from those seen in atherosclerosis The very term aging is a vague concept which involves many unknown elements, some or all of which may be subject to modification or control

For these various reasons the fatalistic assumption that atherosclerosis is an inevitable and inexorably progressive process should be *abandoned It is more probable that athero*sclerosis represents a disease process due to definite physical and chemical factors More fruitful results will be obtained if concentrated efforts are directed toward discovering and mastering these etiologic elements

METABOLIC THEORY OF ATHEROSCLEROSIS

One of the widely held theories of atherosclerosis relates its origin to a disturbance in lipid metabolism and more specifically in the metabolism of cholesterol The detailed evidence for this theory presented below, is based chiefly on the cholesterol content of human atherosclerotic lesions and on the development of hypercholesterolemia and atherosclerosis in many experimental animals following cholesterol feeding Many variants of this theory have been proposed Aschoff[11] believed that cholesterol and other lipids entered the arterial intima from the plasma by a process of imbibition and subsequently cholesterol ester and free cholesterol were deposited and retained in altered intimal tissue [21] The plasma is thought to pass into the intima by trans-endothelial imbibition and to filter through the artery from intima to adventitia where it is reabsorbed into the vasa vasorum The deposition of lipids or lipoproteins in the intima and the consequent development of atherosclerotic lesions may depend on the following factors (1) the plasma content of lipids or lipoproteins their concentration and physicochemical characteristics, (2) the arterial blood pressure and other mechanical factors which promote the filtration of lipids as lipoproteins from plasma through arterial wall, and (3) the structure and function of the arterial tissue, especially the intima which may determine whether lipoproteins are deposited and the responses of the intima to their degradation products Tissue permeability may also be a significant factor [illegible]

Anitschkow [3] among others, emphasized the primary importance of hypercholesterolemia in the deposition of cholesterol in the intima Leary[127] assumed that macrophages in the liver and other reticuloendothelial tissues accumulate cholesterol travel through the blood stream as cholesterol containing foam cells and penetrate the intima through spaces between the endothelial cells According to Leary the accumulation and disintegration of these lipophagic foam cells in the intima *result in soft lipoidal atheromata which are* characteristic of atherosclerosis According to Winternitz et al [illegible] the development of atherosclerosis depends on the presence of intimal capillaries which rupture and give rise to hemorrhages The extravasated blood is presumed to be the source of the cholesterol which leads ultimately to atheroma and necrotic intimal thickenings However, the existence of intimal capillaries in the normal vessel is uncertain, it is more probable that they arise secondarily after the atherosclerotic process has been initiated

Hueper[100] contended that colloidal imbalance in the plasma leads to the precipitation of the cholesterol as a film on the intima Consequently intimal nutrition by way of the vascular lumen is impaired This

results in subendothelial intimal anoxia injury and increased permeability of the endothelial cells and the infiltration and deposition of cholesterol from the serum This theory professes that the initial disturbance in atherosclerosis is one of instability of the dispersion of cholesterol in the blood due either to hypercholesterolemia or alteration in other substances in the blood which diminish the solubility of cholesterol This concept is based in part on the experimental production of atherosclerosis not only by cholesterol but also by polyvinyl alcohol methyl cellulose and similar macromolecular substances which impair the plasmatic colloidal equilibrium

EVIDENCE FOR METABOLIC THEORY

The metabolic theory is based chiefly on

(1) Pathologic and chemical studies of the atherosclerotic lesions

(2) Experimental production of atherosclerosis by feeding cholesterol

(3) Plasma lipids and lipoproteins

(4) Frequency and severity of atherosclerosis in association with diseases accompanied by hypercholesterolemia

(5) Purported rarity of atherosclerosis among people whose diet contains little or no animal fat (cholesterol)

Although the evidence is based on a vast array of studies and observations the reader is cautioned not to be carried away by the sheer number of these studies many of which are essentially repetitions which do not significantly amplify basic knowledge Much of the evidence is circumstantial and indirect One should constantly inquire whether the observations reported have a direct bearing on the pathogenesis of atherosclerosis *as it occurs in man* Two common assumptions which are made in interpreting experimental and other observations and which may or may not be valid are (1) that hypercholesterolemia or other alteration in plasma lipids is an index of the presence of significant atherosclerosis and that factors correcting hypercholesterolemia also retard or alleviate atherosclerosis and (2) that experimental atherosclerosis induced by cholesterol feeding alone or in combination with other factors may be regarded as essentially identical with human atherosclerosis and that factors which cause retard or reverse experimental atherosclerosis would also similarly influence human atherosclerosis A major difficulty in studies of human atherosclerosis is the inability to discover its presence until it is very advanced consequently one cannot assume that clinical disease may be employed as an accurate gauge of atherosclerosis Widespread atherosclerosis may be present when there are no clinical manifestations

1 Pathology and Chemistry of Atherosclerotic Lesions

Pathologic and chemical studies of atheromatous lesions have emphasized the presence of large amounts of lipids notably cholesterol esters and free cholesterol [337] The quantity exceeds that which can be explained by local degeneration [181] The concentrations of the various lipids correspond closely to their concentration in the plasma suggesting that they reach the intima by non selective infiltration or imbibition from the plasma [135, 97] In early lesions there is an increase in total lipids including free cholesterol and cholesterol esters phospholipids (lecithin and sphingomyelin) and neutral fat With the occurrence of degeneration and the development of advanced lesions most of the lipids diminish in concentration whereas cholesterol esters predominate Of special interest is the relatively high concentration of dihydrocholesterol (10 per cent of the cholesterol fraction) a metabolic product ordinarily secreted by the intestine and excreted in the feces since it is not reabsorbed The unstable lipids in the plasma are transported as lipoproteins chiefly beta lipoprotein After this is filtered from plasma to the vascular intima the filtered lipoprotein breaks down leaving the lipid to which intimal tissues react as if it were an inert foreign body Most of the soluble amino acids fatty acids and lipoproteins passing through the arterial wall are resorbed by the adventitial capillaries and lymph Pathologic observations strongly suggest that the baneful consequences of atherosclerosis are largely due to the deposits of cholesterol esters in the intima and the secondary reactions to its presence (p 430)

2 Experimental Atherosclerosis

Atheromatous vascular lesions resembling those of human atherosclerosis have been produced experimentally in rabbits guinea pigs hamsters pigs and chickens by feeding large quantities of cholesterol or animal fat [10 ... 115] A pronounced hypercholesterolemia precedes the development of the atheromatous lesions

and is presumed to be the primary disturbance leading to intimal cholesterol deposition The experimental production of hyperlipemia and early atherosclerosis in rabbits by a high vegetable fat diet has also been reported [redacted]

Many objections have been raised to the validity of applying these experimental observations to the explanation of human atherosclerosis[44, 173] The rabbit is an herbivorous animal man is omnivorous Attempts to produce atherosclerosis by cholesterol feeding in a variety of carnivorous or omnivorous animals have been very difficult and the distribution of atherosclerotic lesions in herbivorous animals differs from that in human atherosclerosis The quantity of cholesterol fed to rabbits [redacted] proportionately far in excess of that usually taken by man and the resulting hypercholesterolemia has no counterpart in the majority of cases of human atherosclerosis Atherosclerosis in man appears to be related more to the arterial reactions, degeneration and repair than to the level of serum cholesterol which is the determinant in the rabbit The lesions of experimental atherosclerosis in the rabbit are chiefly in the reticuloendothelial tissues and parenchymal organs and not as prominent in the coronary or cerebral arteries as in human atherosclerosis However, some of these objections to any analogy between experimental atherosclerosis in rabbits and human atherosclerosis appear to have been overcome by the experimental production of a generalized atherosclerosis in the omnivorous dog, by means of daily feeding of cholesterol after modification of thyroid function by thiouracil[204] or radioiodine administration or after production of renal hypertension Atheromatosis produced in chickens by subcutaneous implantation of diethylstilbestrol [7] and in the rhesus monkey by maintaining pyridoxine deficiency,[180] or by feeding cholesterol with diets low in sulfur containing amino acids[123] also resembles human atherosclerosis particularly in that the cerebral and coronary arteries are involved On the other hand, atheromatosis has not been produced in rats by feeding diets which are atherogenic in other specie But atherosclerotic lesions have been produced in the rat by feeding cholesterol and methyl thiouracil after having induced renal hypertension It will be noted that in many species cholesterol feeding is effective in producing atherosclerosis only when thyroid function is simultaneously depressed, renal hypertension is established or the cholesterol is administered in diets deficient in certain respects (pyridoxine sulfur amino acids)

3 Plasma Lipids and Lipoproteins and Atherosclerosis

The relation of experimental atherosclerosis to hypercholesterolemia has stimulated extensive investigations of blood lipids in humans and their possible connection with human atherosclerosis

The *blood lipids* include chiefly

(a) Neutral fats—esters of fatty acids and glycerol

(b) Phospholipids (phosphatides)—fats which contain in addition phosphoric acid and nitrogenous groups such as choline The phospholipids include chiefly lecithin but also the cephalins and sphingomyelin

(c) Cholesterol—hydrogenated phenanthrene derivatives The plasma cholesterol is a steroid with an iso-octyl chain at carbon 17 About 70 per cent of it is normally in the ester form as a result of combination with fatty acids mostly unsaturated, attached to carbon 3

The total plasma lipids amount to about 700 mg per 100 cc of which total cholesterol forms about 33 per cent and the phospholipids about 35 per cent, the remainder is neutral fat

All of the lipids in the blood are transported in combination with proteins, as lipoprotein complexes (p 422) which serve to maintain the lipids in colloidal solution in the blood

Plasma Cholesterol and Atherosclerosis Efforts to discover hypercholesterolemia in humans with coronary or other forms of vascular atherosclerosis have yielded contradictory results[6] [redacted] Lande and Sperry[10] found that determinations of plasma cholesterol after accidental death revealed no difference between individuals with extensive atherosclerosis and those without such vascular disease On the other hand, Davis et al[43] observed higher values for blood cholesterol and other lipids in a group of patients with angina pectoris presumably due to coronary atherosclerosis than in a group of control patients But there was a wide range of values and considerable overlapping of individual values in both groups in these and other studies[14] Barker[1] likewise found a

higher mean level of plasma lipids in cases of arteriosclerosis obliterans than in normal controls but the range in both groups was essentially similar Like the incidence of atherosclerosis the concentration of serum cholesterol tends to rise with age but not in all persons nor in peoples of all countries [115]

Of possibly greater significance are the findings of Steiner and Domanski[203] who studied the cholesterol levels of 15 patients with coronary atherosclerosis and of 15 normal subjects at frequent intervals for periods up to two years In the former group they observed a distinctly higher average serum cholesterol but especially noted that it was inconstant and fluctuated widely while the values in normal subjects remained relatively constant Since atherosclerosis requires a long period of development isolated determinations of the blood cholesterol may not reflect intermittent variations Since the normal content of serum cholesterol is close to its saturation point deposition of cholesterol may follow slight elevations above normal levels The interpretation of reported values for serum cholesterol is obscured by technical difficulties in the methods for cholesterol determination and by uncertainty as to the range of normal Furthermore since atherosclerosis is widespread at a relatively early age whereas clinical manifestations appear relatively late many of the individuals serving as normal controls who have hypercholesterolemia may quite possibly have clinically latent atherosclerosis

Moreton proposed the theory that the cumulative effect of numerous fatty meals produces transient showers of large lipid particles (chylomicrons) which are deposited in the arterial intima and may lead to atherosclerosis [147] The neutral fats and fatty acids are more readily removed and resorbed by macrophages and tissue enzymes than the large lipid particles which accumulate to form atheroma

The Plasma Cholesterol Phospholipid Ratio and Atherosclerosis In recent years emphasis on total serum cholesterol as an index of atherosclerosis has diminished somewhat and attention has been shifted to (1) the plasma cholesterol phospholipid ratio (2) the concentration of plasma alpha and beta lipoproteins or the percentage of cholesterol in alpha and beta lipoproteins and (3) the concentration of lipoprotein molecules of specific size in the plasma as disclosed by the analytical ultracentrifuge It should be emphasized that the abnormal lipid or lipoprotein values and relationships are *not* present in all atherosclerotic individuals and that there is considerable overlapping between normal and atherosclerotic individuals

Ahrens and Kunkel[3] suggested that the ratio of cholesterol to phospholipid concentration was an index of the stability of lipid solutions in the blood and that this cholesterol phospholipid ratio not the cholesterol concentration alone was a determining factor in the development of atherosclerosis Cholesterol is insoluble in aqueous solution but phospholipids tend to keep it in solution in the blood Elevation of the cholesterol phospholipid ratio may predispose to the precipitation of cholesterol in the arterial intima

In normal rabbits the cholesterol phospholipid ratio is less than 1 in rabbits with atherosclerosis induced by cholesterol feeding the ratio is greater than 1 [184] In species such as the dog in which significant atherosclerosis does not appear spontaneously and is difficult to produce experimentally the proportion of cholesterol to phospholipid is much lower than in man But when atherosclerosis is produced experimentally in the dog by combining thiouracil with cholesterol feeding the cholesterol phospholipid ratio rises considerably [40] The inhibition of experimental atherosclerosis in cholesterol fed rabbits by the production of alloxan diabetes was associated with a much greater elevation in serum phospholipids than in serum cholesterol and therefore with a reduction in the cholesterol phospholipid ratio [17, 41, 27] A similar reduction in the cholesterol phospholipid ratio occurred when atherosclerosis was inhibited in the cholesterol fed rabbit by cortisone [75] or in the cholesterol fed chick by stilbestrol [170]

The plasma cholesterol phospholipid ratio has also been correlated with human atherosclerosis Gertler Garn and Lerman[80] found the average serum cholesterol phospholipid ratio significantly higher in patients who had survived a coronary artery occlusion than in normal young men of comparable age Steiner and associates [94] found that the serum cholesterol and serum phospholipid but also the cholesterol phospholipid ratio were increased in most of 82 patients with clinical coronary atherosclerosis However in many

persons with coronary occlusion the cholesterol phospholipid ratio is in the normal range, and Wilkinson [illegible] found that the cholesterol phospholipid ratio was not significantly different in patients with clinical atherosclerosis from that in patients in a large miscellaneous group Furthermore he observed that the cholesterol phospholipid ratio was dependent exclusively on the cholesterol level unless there was hepatic insufficiency

The hypothesis that atherosclerosis is related to the physical state of the blood lipids or lipoproteins has led to the study of other agents which like the *phospholipids may influence* lipid solubility The injection of surface-active agents, such as the detergents Tween 80 and Triton A 20 into cholesterol fed rabbits not only caused a marked sustained elevation in serum phospholipid but also greatly inhibited the development of atherosclerosis[166, 107] Metal binding agents such as the chelator EDTA and hydralazine were found to cause a prompt fall in plasma cholesterol in man[88]

There has been a renewal of interest in the observation of Hahn[85] that an injection of heparin cleared the postprandial lipemic serum of the dog but was ineffective in vitro Anderson and Fawcett[7] showed that the injection of heparin led to the formation of another substance surface active heparin phospholipid complex, which was actually responsible for the clearing Anfinsen et al [8] found the clearing factor to be a protein complex containing no free heparin but liberating it on boiling The protein complex was inactivated by protamine

Heparin was reported to retard the development of atherosclerosis in cholesterol-fed rabbits and to diminish the concentration of the atherogenic beta lipoproteins[154] and the S_f 10–50 lipoprotein aggregates[79] But these findings were not confirmed by Herbst et al[92] It was found that alimentary lipemia was cleared by an injection of a 3 mg dose of heparin more readily in normal individuals than in atherosclerotic patients The formation of heparin has been related to the mast cells which are dispersed around blood vessels[36] Mast cells were found to be abundant *in animal species such as the rat*, in which it is difficult to produce atherosclerosis, and relatively sparse in the rabbit in which atherosclerosis is readily produced[36] A lower count of mast cells was found in elderly females than in young female adults, and in atherosclerotic individuals than in non atherosclerotic individuals[27])

Sulfated alginic acid, a synthetic analogue of heparin, was reported to inhibit the hypercholesterolemia and atherosclerosis usually caused by cholesterol feeding in rabbits [illegible]

Plasma Lipoproteins and Atherosclerosis Although the various plasma lipids are identified individually and their concentrations determined by chemical means, they do not circulate as such in the blood plasma but are transported in combination with proteins as *lipoproteins* The *standard methods for* determining plasma lipids utilize organic solvents which precipitate the protein moieties and extract the lipids free of protein Lipoproteins are not well defined chemical entities of uniform stoichiometric composition They are segregated and identified directly or indirectly by (1) salt fractionation of plasma proteins (2) electrophoresis of blood plasma, (3) alcohol fractionation of plasma proteins, or (4) flotation in the ultracentrifuge

(1) *Plasma albumin can be separated from* the globulins by precipitation of the latter with 50 per cent saturated ammonium sulfate or 22 per cent concentration of sodium sulfate The globulins are separated into euglobulin, pseudoglobulin I and pseudoglobulin II by precipitation with various concentrations of sodium sulfate (13 5, 17 5 and 21 5 per cent, respectively) The alpha and beta lipoproteins are associated with both pseudoglobulin I and II

(2) *Electrophoresis separates* the various plasma proteins, which differ in the magnitude of their electrical charge by differences in their speed of migration in an electrical field *In this manner*, albumin alpha globulins, beta globulin and gamma globulin are differentiated The alpha and beta lipoproteins are the lipoproteins which migrate with the same speed as the alpha and beta globulins respectively More specifically they are termed $alpha_1$ and $beta_1$ lipoproteins [illegible] Recently, the simple, inexpensive rapid technique of paper electrophoresis has been used whereby the various serum proteins migrate in an electrical field set up across a strip of filter paper saturated with buffer[101] A column of starch has been similarly employed in the separation of plasma proteins by zone electrophoresis[115]

(3) *The Cohn method of fractionation of*

plasma utilizes the variable solubility of various protein fractions in different concentrations of ethyl alcohol (14.25 to 19 per cent) at low temperatures (minus 5° C.) at varying pH, ionic strength and protein concentration. Cohn's fraction V contains plasma albumin, fraction IV contains the alpha$_1$ globulin (and alpha$_1$ lipoprotein), fraction III, especially III, contains the beta$_1$ globulin (and beta$_1$ lipoprotein).

The plasma cholesterol and the phospholipids are carried as alpha and beta lipoproteins. But only about 25 to 30 per cent of the total cholesterol in humans forms part of alpha lipoprotein, whereas 70 to 75 per cent of the plasma cholesterol is found in the beta lipoprotein fraction.[160] By contrast, in species relatively resistant to atherosclerosis the percentage of cholesterol is high in the alpha lipoprotein and low in the beta lipoprotein fraction. The percentage of total cholesterol in the alpha lipoprotein is highest in young and normal humans, diminishes with age and is lowest in patients with disease predisposing to atherosclerosis and in those who have survived a myocardial infarction.[11]

The ratio of cholesterol to phospholipids in plasma alpha lipoproteins averages 0.5, whereas the cholesterol phospholipid ratio in the fraction containing the beta lipoprotein averages more than 1.0.[illegible, 160] Thus if an elevated plasma cholesterol concentration or a high cholesterol phospholipid ratio contributes to the development of atherosclerosis, then the latter is also favored by elevated concentrations of beta lipoprotein with its high cholesterol and high cholesterol phospholipid ratios. The ratio of beta to alpha lipoprotein as well as the percentage of cholesterol in the beta lipoprotein fraction increases with age and is increased in patients who have recovered from a coronary thrombosis. These changes in lipoprotein concentration were found to correlate more closely with clinical coronary atherosclerosis than an elevation in plasma cholesterol or the cholesterol phospholipid ratio. The correlation of atherosclerosis with relative and absolute increase in the beta lipoprotein fraction may be related to lesser stability of the beta lipoprotein fraction than the alpha and consequently greater probability of dissociation and deposition in the arterial intima.

(4) The plasma lipoproteins may also be differentiated by the ultracentrifuge in which the strong gravitational force floats the large protein molecules to the surface at velocities related to their molecular weight and the specific gravity of the solution. The density of the plasma sample is first increased to 1.063 at 26° C. by the addition of sodium chloride (or to 1.21 by the addition of potassium bromide). The lipoproteins which are of lower density than ordinary proteins are then readily made to migrate (float) toward the axis of rotation of the ultracentrifuge. By the use of optical scanning devices and photography, the migrating boundaries and quantities of the individual plasma proteins of different molecular weights can be observed and photographed. The lipoproteins are designated in terms of S_f units (Svedberg flotation units), a unit denoting a migration rate of 10^{-13} cm. per second per dyne per gm. A lipoprotein which migrates (floats up) at ten times the above rate of speed is identified as a lipoprotein of the S_f 10 class.

By studying the flotation of plasma lipoproteins in the ultracentrifuge, Gofman and associates[73, 104] found an entire series or "spectrum" of lipoproteins varying in flotation rate from S_f [illegible] to S_f 4000. They found evidence that patients with clinical coronary atherosclerosis have a high concentration of S_f 12–20 lipoprotein much more often than normal individuals. Later a similar correlation was made between atherosclerosis and lipoproteins of the S_f 20–200 classes. The S_f 12–20 lipoproteins and to a lesser degree those of the S_f 20–200 class were regarded as atherogenic since their concentration was found to be greater in males than females, increased with age and in those with a history of coronary occlusion, and rose with the experimental production of atherosclerosis in rabbits. The correlation between S_f 12–20 and S_f 20–200 lipoprotein levels and atherosclerosis was reported to be two to four times as great as that of serum cholesterol levels and atherosclerosis,[illegible, 104] although this has been refuted by Keys.[109] Low cholesterol, low fat diets and the injection of heparin, which were thought to influence atherosclerosis favorably, also altered the lipoprotein pattern toward normal. Gofman and associates[73] have actually claimed the ability to assess the degree of probability that an individual had experienced or was apt to experience sig

nificant clinical coronary disease Most of these claims are unsubstantiated at the present time some studies testing these claims have not yet been reported There is considerable overlapping of the so called atherogenic lipoprotein classes in normal and atherosclerotic individuals and considerable error in attempting to correlate the concentration of various S_f classes of lipoproteins with clinical atherosclerosis

The relationship of lipoproteins to atherosclerosis is considered chiefly from the view point of its cholesterol and other lipid content and distribution The possibility must also be considered if such a lipoprotein atherosclerosis relationship exists that it is the protein moiety which accounts for the disturbance leading to lipid deposition and atherosclerosis It is of interest that atherogenesis in cholesterol fed monkeys is augmented by a diet deficient in sulfur containing amino acids

Cholesterol Metabolism and Atherosclerosis [196, 187, 74] With growing interest in the possible relation of cholesterol and hypercholesterolemia to atherosclerosis and with the availability of radioisotopic techniques, investigations of cholesterol metabolism have assumed increasing importance These studies are concerned with the interrelationship of dietary intake (exogenous) cholesterol the synthesis of (endogenous) cholesterol degradation of cholesterol excretion of cholesterol and the metabolism of cholesterol within different organs and tissues notably the aorta

The dietary intake of cholesterol by the human adult is about 200 to 500 mg daily and varies particularly with the intake of animal fats This compares with the ability to synthesize 1 5 to 2 0 gm daily from various sources [77] Cholesterol absorption is aided by ingested fats and especially by secreted bile The cholesterol is chiefly absorbed by the lymphatics and enters the blood stream where it is transported in combination with alpha and beta globulins as alpha and beta lipoproteins According to Friedman and Byers [81] endogenous and dietary (exogenous) cholesterol exist in plasma in different states and are handled differently The absorption of cholesterol from the intestine includes not only dietary cholesterol but also 0 5 to 1 5 gm of cholesterol excreted by the liver in bile Cholesterol absorption may be impaired by low fat diets, sitosterols and other agents

The liver is the major organ concerned with cholesterol which it can synthesize store and destroy [77, 81] By these processes it largely determines and controls the level of serum cholesterol The latter is maintained fairly constant by some homeostatic regulation of the dynamic equilibrium between the absorption and synthesis of cholesterol on the one hand and the metabolism and excretion on the other [76] Cholesterol esters (i e , cholesterol esterified with fatty acids) are formed essentially in the liver with the aid of enzymes and constitute 70 per cent of total plasma cholesterol However studies with C^{14} labeled cholesterol have shown that most tissues beside the liver can synthesize cholesterol, especially the adrenal gland [199, 77, 213]

Cholesterol is synthesized in the human even in the absence of dietary cholesterol [21, 81] from acetate acetoacetate pyruvate butyrate and stearate which in turn are derived from dietary carbohydrates proteins and fats The acetate fragments are esterified with the thiol group of coenzyme A to form acetyl coenzyme A, the active acetic acid Coenzyme A may be concerned with both the synthesis and degradation of cholesterol The exact steps in the synthesis of acetate into cholesterol are uncertain but studies with radioactive isotopes indicate that the unsaturated hydrocarbon squalene is an intermediate [181, 187] When the dietary intake of cholesterol is increased endogenous synthesis is inhibited or when the former is diminished cholesterol synthesis is increased [81] Consequently it is difficult to lower serum cholesterol for sustained periods by limiting cholesterol intake There is evidence that in the rat cholesterol synthesis is inhibited by estrogens and augmented by corticosteroids

Cholesterol is oxidized in the body to carbon dioxide by many tissues but most actively by the liver Some of the cholesterol is converted into steroid hormones and most of it into bile acids which are excreted in the bile Cholesterol may be disintegrated to dihydrocholesterol by direct reduction or to dihydrocholesterol or coprosterol through the intermediate cholestenone Thirty one per cent of the iso-octyl side-chain carbon is eliminated as carbon dioxide in the expired air [76] whereas none of the ring carbon appears as carbon dioxide, it is recovered in the saponifiable fraction of the fecal steroids Cholesterol itself and its products, dihydro

cholesterol and coprosterol, which are poorly absorbed are excreted in the feces

There are considerable data indicating that blood vessels participate actively in metabolism and that the aortas of various species are capable of synthesizing cholesterol from acetate and of oxidizing it to carbon dioxide These observations have raised the question whether and to what extent atherosclerosis i e the deposition of cholesterol in arteries is secondary to faulty arterial metabolism

Studies of cholesterol metabolism have not yet disclosed whether or not atherosclerosis is fundamentally an inborn or acquired metabolic disturbance with respect to this substance Such a metabolic disturbance could produce atherosclerosis if (1) there was excessive cholesterol synthesis beyond the quantity which could be catabolized or excreted (2) there was excessive absorption of *cholesterol or diminished excretion, (3) there* were abnormalities in its combination as lipoproteins or in its transport in the blood stream resulting in impaired stability of cholesterol colloids and consequent deposition in the arterial walls or (4) there was interference with the transit of cholesterol through the arterial wall due to mechanical factors or to impairment of vessel metabolism The last possibility would suggest that primary abnormalities in the structure or function of vessels are more important than disturbances in cholesterol metabolism in the development of atherosclerosis

4 Atherosclerosis in Diseases with Hypercholesterolemia

The frequency severity and precocity of coronary atherosclerosis in diseases associated with hypercholesterolemia add considerable support to the cholesterol theory of atherosclerosis In the cases of *familial xanthomatosis with hypercholesterolemia* there is an unusually high incidence of angina pectoris coronary occlusion and death at an early age because of severe coronary atherosclerosis Genetic analysis is said to support the concept that familial xanthomatosis is a disturbance in *cholesterol or lipid metabolism which is* inherited as an incomplete dominant mendelian trait Xanthomatous lesions occur only in patients who are homozygous i e carry two abnormal genes with respect to the cholesterol disturbance [■ 333] Heterozygous individuals with only one abnormal gene, have only hypercholesterolemia or less severe manifestations of xanthomatosis The theory has been proposed that coronary atherosclerosis likewise represents a related inborn error of lipid or cholesterol metabolism, manifested by an elevated serum cholesterol[2] This concept is based largely on the high incidence of hypercholesterolemia in patients with coronary atherosclerosis below the age of 50 but also in the finding of hypercholesterolemia in one third to one half of the siblings of such patients[2] However the relationships are statistical not universal and the analogy to familial xanthomatosis may be quite superficial and fortuitous The arbitrary choice of normal values for serum cholesterol the effect of diet race and possible other factors in the level of serum cholesterol, the overlapping of normal and elevated serum cholesterol levels in presumably normal persons and in those with coronary atherosclerosis *as well as the unproven assumption* that hypercholesterolemia causes and ■ an index of human atherosclerosis are among the difficulties or objections to acceptance of the above theory that coronary atherosclerosis is closely related to or is a mild form of familial hypercholesterolemia

Essential hyperlipemia is likewise thought to be frequently associated with premature atherosclerosis[194] but if atherosclerosis is present hypercholesterolemia is usually also associated

The etiologic relationship of diabetes to premature and advanced atherosclerosis is discussed elsewhere (p 1034) The frequency of advanced atherosclerosis in youthful diabetics and *atherosclerotic* coronary *thrombosis in* diabetic women in contrast with its infrequency among nondiabetic women are unexplained observations which are among the most important clues we possess to the cause of atherosclerosis Rabinowitch[77] and others have associated the high incidence of atherosclerosis among diabetics with hypercholesterolemia in the more severe and poorly controlled cases But Man and Peters[131] found that atherosclerosis with or without hyper*tension* occurred *in 79* diabetic patients whether the blood cholesterol was normal or abnormal

Premature atherosclerosis in diabetes was formerly attributed to the high fat diets in the pre-insulin era But there has been no demonstrable reduction in the incidence or severity of atherosclerotic complications de

spite the use of high carbohydrate diets and better control of fat and carbohydrate metabolism with insulin In fact by prolonging the lives of diabetic patients, such measures permit more of them to survive long enough to become victims of atherosclerosis (p 1031) *Nevertheless evidence has been* presented that among young diabetics who had survived twenty years of diabetes 74 per cent of those incapacitated by atherosclerosis of the heart eyes or kidneys had repeatedly experienced coma, while only 17 per cent of those without atherosclerosis had experienced coma [5] The specific metabolic or endocrine factor in diabetes which predisposes to atherosclerosis remains uncertain

Severe coronary atherosclerosis is said to be a common finding in cases of myxedema, which is characteristically associated with hypercholesterolemia [5] (p 1017)

5 Relation of Atherosclerosis to Diet

Two types of studies have related the dietary intake of cholesterol to the development of atherosclerosis (1) The quantity of cholesterol intake has been correlated with the level of serum cholesterol or lipoproteins, which is presumed to be an index of atherogenesis (2) *The incidence of morbidity and* mortality from atherosclerosis has been correlated with the cholesterol intake by various ethnic groups in different geographic regions or under different economic political circumstances

Cholesterol Intake and Serum Cholesterol This problem is *complicated by a frequent* failure to distinguish between high cholesterol and high fat intake since foods rich in fats are usually but not invariably high in cholesterol content Cholesterol is found in fats of animal origin but not in vegetable fats In man cholesterol feeding produces little or no change in plasma cholesterol and there is little correlation between serum cholesterol and cholesterol *in the diet over a wide range of* intake [11, 234, 69] Only with extreme reductions in cholesterol and fat intake (20 gm of fat and virtually no cholesterol) is the serum cholesterol reduced [20, 135] On the other hand, when vegetable fat containing no cholesterol was added to such a low cholesterol, low fat diet the previously lowered plasma cholesterol returned to its original higher level [85, 136] The conflicting *observations of Kinsell et* al [116] *regarding the influence of vegetable fat* may be related to the type of vegetable fat employed (p 437) Only highly unsaturated *fats may produce a significant reduction in* serum cholesterol According to Jones et al [102] the so-called atherogenic Sf12–20 lipoproteins diminish markedly in individuals on a low fat and low cholesterol diet

According to Keys et al, *the serum cho*lesterol level and the cholesterol content of the diet in Minnesota are unrelated [11] When the cholesterol intake of middle-aged men was reduced by 50 per cent or more for a year, the serum cholesterol levels remained unaltered On the other hand there was a rapid decline *in the serum cholesterol when these subjects* were placed on cholesterol free, fat free diets Observations of the Eskimos in the Aleutian Islands also indicate that the serum cholesterol is not significantly influenced by cholesterol in the diet Although these individuals subsist on a fairly uniform high *protein fish diet which contains little cho*lesterol their serum cholesterol levels did not differ from that of adult Americans and in 4 of 81 there was hypercholesterolemia [83] Garn and Gertler[83] concluded that endogenous mechanisms and not dietary cholesterol intake were responsible for the level of serum cholesterol *It now appears that the dietary* intake of fat and not of cholesterol per se exerts a strong influence on serum cholesterol Populations habitually subsisting on low fat diets as in Italy, Spain and certain parts of Africa, have a relatively low plasma cholesterol, and the plasma cholesterol level *does not rise and may fall with age* in contrast with the findings in this and other countries in which the intake of fat is high [115] [116] In a recent study the serum cholesterol and beta lipoprotein concentrations of rural Central American subjects who take a vegetarian diet very low in fat were compared with the corresponding serum constituents in urban Guatemalan and North *American subjects on a relatively* liberal fat diet [134] The serum cholesterol was found to be significantly lower in the group on a low fat diet but the lipoprotein levels in the three groups were variable and not significantly different

Cholesterol Intake and Atherosclerosis The occurrence of atherosclerosis in man has also been related to the dietary intake of fat, *rather than of cholesterol* Studies of the dietary intake in various countries and climates *have been interpreted to indicate a higher*

rate of atherosclerosis among people consuming a diet high in fat than among those on a low fat diet[208, 183] Snapper[186] commented on the rarity of advanced atherosclerosis among the northern Chinese who subsist on cereals and omit animal fats A similar paucity of atherosclerosis among the Okinawans and Costa Ricans was attributed to their low intake of cholesterol-containing food

In a Cape Town province the Bantus obtain 16 per cent of their calories from fat the Negroes 25 per cent and the local Europeans like persons in the United States obtain 40 per cent of their calories from fat[114] Severe atherosclerosis and myocardial infarction is very rare among the Bantus fairly frequent among the Cape Province Negroes and very common among the Europeans Within each of the groups the serum cholesterol was found to be directly related to dietary fat intake Aschoff[11] reported a sharp diminution in atherosclerosis in Germany following World War I when the populace was ingesting a particularly low fat diet Similarly in Norway and other European countries in World War II there was a sharp reduction in morbidity and mortality from clinical atherosclerosis including coronary heart disease presumably due to the great reduction in fat and cholesterol in the diet[44, 330, 209a] The incidence of clinical atherosclerosis rose rapidly following restoration of a more normal food intake Similarly when the Jews from Yemen where they subsisted on a low fat diet and experienced little coronary heart disease emigrated to Israel where their diet became rich in fats their serum cholesterol rose and the incidence of coronary heart disease increased significantly[159a] These reports on the relation of diet and atherosclerosis are suggestive but suffer from an inadequacy of statistical data and a multiplicity of factors besides dietary intake which may be concerned

A low serum cholesterol and a low incidence of coronary heart disease in a given racial group are not invariably associated with a low fat diet Thus it was found that coronary heart disease is rare among the Navajo Indians Nevertheless despite the relatively high incidence of coronary heart disease and the higher serum cholesterol levels among control subjects in Cleveland the dietary habits of the Navajo Indians did not differ from those of the control subjects[184] These observations were interpreted as suggesting that heredity, rather than the diet was the most likely explanation for the low levels of serum cholesterol and the low incidence of coronary heart disease among Navajo Indians

ENDOCRINE FACTORS

Gonadal Hormones

One of the most striking features of coronary atherosclerosis is the pronounced predilection for the male sex especially in the absence of diabetes or hypertension in the female Any satisfactory theory of atherosclerosis should explain this difference The purported difference in thickness of the arterial intima in the two sexes has not been substantiated The possible relationship to differences in tobacco intake has not been adequately explored The possible relationship of the sex hormones to atherosclerosis is indicated by studies of the serum lipoproteins in the two sexes by experimental observations on the effect of estrogenic hormones and by other pertinent findings

It has been found that normal young women, in whom coronary occlusion is rare have a relatively smaller amount of beta lipoprotein and a higher concentration of alpha lipoprotein than normal young men but this sex difference is no longer apparent after the menopause[166, 184] Correspondingly the atherogenic lipoproteins of the Sf10–100 classes in the ultracentrifuge are likewise found in lower concentration in young women than in young men[10] The sex differences with respect to serum lipoproteins are absent when women suffer from atherogenic diseases such as diabetes nephrosis or familial hypercholesterolemia (These observations suggested that estrogenic hormones might influence the development of atherosclerosis by their effect on the distribution or nature of the plasma lipoproteins)

Postmortem observations have been interpreted as linking atherosclerosis to gonadal influences The incidence and severity of coronary atherosclerosis in bilaterally oophorectomized women is greater than in control females and approximates that in men of the same age range Conversely the incidence and severity of atherosclerosis was much less in men treated with estrogens for carcinoma of the prostate than in control series[181]

The administration of estrogens inhibits the development of cholesterol induced coronary

atherosclerosis in cockerels[105] Estrogens were also capable of *reversing* coronary atherosclerosis induced experimentally by cholesterol feeding[170] Estrogens administered to premenopausal and postmenopausal women caused a reduction in both the serum cholesterol and the serum cholesterol phospholipid ratio[53] Gertler[65] observed that the administration of 500 mg of stilbestrol to 25 men following bilateral orchidectomy for carcinoma of the prostate resulted in an increase in serum phospholipid without change in the serum cholesterol level Other observers[157, 205] reported a significant fall in serum cholesterol or cholesterol ester and in the cholesterol phospholipid ratio without change in or with elevation of the phospholipid level in patients with a previous myocardial infarction who received 0 25 mg to 1 mg of ethinyl estradiol (Estinyl) daily

Extensive studies of the effect of estrogens on serum lipids were made by Barr and associates[15, 188] They administered 1 mg daily of ethinyl estradiol or its equivalent, as Premarin or other estrogen to survivors of acute myocardial infarction The abnormal elevation of the beta lipoprotein fraction and the increased percentage of total cholesterol in this fraction were largely or totally corrected following estrogen administration At the same time there was a reduction in serum cholesterol and an increase in serum phospholipid, and consequently a fall in the cholesterol phospholipid ratio from a mean of 1 05 to 0 72 The effects were maximal in 8 weeks When androgens were administered simultaneously in an effort to neutralize the unpleasant side effects of the estrogens, the effects of the latter in plasma lipids were diminished or obliterated This is in contrast to the findings of Stamler et al[201] that the combination of estrogens and androgens administered to the cholesterol fed chick prevented the development of atherosclerosis

Other Hormones

Thyroid relationships to atherosclerosis have been noted Depression of thyroid function by thiouracil enabled the production of atherosclerosis by cholesterol feeding in the previously resistant dog[208] Thyroid administration inhibits experimental atherosclerosis in the cholesterol fed rabbit[217] or chick[203] Large doses of thyroid (10 grains daily), administered to schizophrenic patients, uniformly lowered serum cholesterol and the "atherogenic" lipoproteins[209] Myxedema is associated with hypercholesterolemia which is thought to predispose to atherosclerosis In hyperthyroidism there is increased intestinal excretion of cholesterol as well as somewhat increased synthesis of cholesterol by the liver The plasma cholesterol is slightly diminished in hyperthyroidism, perhaps because the increased intestinal excretion exceeds the augmented synthesis of cholesterol[6]

Adrenal Cortex The adrenal cortex is concerned with the regulation of cholesterol and other lipid metabolism[91, 4] and may thus play a part in the development of atherosclerosis Cushing's disease due to excessive adrenocortical hormones, is frequently associated with hypercholesterolemia The administration of cortisone has been followed by hyperlipemia and hypercholesterolemia An increased deposition of lipids in both the intima and media of the aorta has been noted in children who had received cortisone or corticotropin But neither cortisone nor corticotropin has favored experimental cholesterol atherogenesis According to Gordon et al[73] and Stumpf and Wilens,[11] experimental atherosclerosis in rabbits is impeded by the simultaneous administration of cortisone with cholesterol A hormonal influence may also be involved in the association of atherosclerosis with diabetes insofar as the latter is related to disturbances in the anterior pituitary, adrenal cortex or pancreatic islets

MECHANICAL FACTORS IN ATHEROSCLEROSIS INTRAVASCULAR PRESSURE AND HYPERTENSION

The localization of atherosclerosis in varying degree in different vascular beds is of great interest Atherosclerosis may be most intense in either the coronary cerebral or peripheral arteries It is not clear why atherosclerosis should involve the vessels in one and not the other area or should involve them to different degrees, when all the vessels are bathed by blood of the same lipid concentrations unless mechanical intravascular factors or differences in vascular structure and function are concerned Similarly, hypercholesterolemia does not cause atherosclerosis of veins This may be attributed to the lower pressure in veins relative to that in arteries But even when phlebosclerosis is associated with high venous pressure the sclerosis consists of hyperplasia and hypertrophy without atheromatous (lip

oidal) intimal deposits. This suggests the importance of the vessel structure or function as well as the chemical composition of the blood and the intravascular pressure in the development of atherosclerosis.

(Many types of mechanical strain or injury have been credited as initiating accessory or aggravating causes of atherosclerosis.[115] Intimal damage is said to result from the constant wear and tear on the blood vessels due to the impact of the intravascular blood pressure. Purported hereditary atherosclerosis is viewed as the consequence of an inherited inferiority of the vascular structure in its ability to withstand these strains. The localization of severe atherosclerotic lesions at the bifurcation of arteries and the mouths of branches is said to be due to the greater impact of the blood at these sites. The severity of atherosclerosis at the site of bifurcation of the left coronary artery into anterior descending and circumflex branches may be related to the size of the angle formed by these branches. Coronary atherosclerosis affects the main epicardial vessels, not the perpendicular penetrating myocardial branches. Greater mechanical strain may account also for the predilection of atherosclerosis for the posterior wall of the aorta where there is greater vascular fixation[179] and for the vessels of the lower extremities as compared to the upper. Such forces as tension, vibration, shearing between intima and media and intimal herniation have been postulated as representing irritant stimuli which damage intimal tissue and provoke proliferation, thickening and secondary atheroma formation.[17, 118] Mechanical intimal injury may be considered as a primary change which predisposes to the deposition of lipid. Or the lipid deposits may be primary while the intimal injury is an accessory factor which is important in determining the localization and intensity of the deposits.)

According to Moschcowitz[151] arteriosclerosis may result from the mechanical effects of the normal systemic intravascular pressure acting over a long period of time. Hypertension representing an elevation of the normal intravascular pressure accelerates and intensifies the arteriosclerotic process. Even when there is hypertension and arteriosclerosis in the greater circulation, arteriosclerosis is usually absent in the pulmonary vessels because, according to Moschcowitz, the pulmonary arterial pressure is only about one sixth of the normal systemic blood pressure. On the other hand pulmonary arteriosclerosis occurs commonly in the presence of long standing mitral stenosis or pulmonary conditions which produce hypertension of the pulmonary circulation.[151] The occurrence of phlebosclerosis in sites of prolonged venous hypertension has been noted.

Abnormalities in the physicochemical structure of the vessel wall or in its metabolic function are probably of major importance in the development of atherosclerosis. Actually relatively little is known concerning such abnormalities and therefore their relation to atherosclerosis has been neglected in comparison to recent emphasis on the possible role of abnormal lipid metabolism.

Assuming that atherosclerosis results from the deposition of lipids in the intima as plasma filters through the arterial wall, increased endothelial permeability or preceding arterial injury may predispose to such deposition of lipids. There is experimental evidence that a variety of types of preliminary vessel injury or other influences modifying structure or function, e.g., sympathectomy or aortic cauterization, have been shown to favor the localization of lipids in the affected area of the vessel and to accelerate the development of atherosclerosis.[44, 166, 199] The intense atherosclerosis found in regions of the aorta involved by syphilis is a striking example of the predisposing influence of underlying disease. If the initial lesion of atherosclerosis is one of intimal hyperplasia and the deposition of mucoid material secondary to the stress of intravascular pressure, such intimal alterations may determine the occurrence and localization of lipid deposits. Injury or change in the intimal elastic membrane may contribute to atherosclerosis since this membrane may act as a barrier to the passage of lipid through the arterial wall.

PATHOLOGY OF CORONARY ATHEROSCLEROSIS

Reviews of the historical development of our knowledge of coronary atherosclerosis have been presented by Benson[15] and by Long.[13] For a detailed description of the gross and microscopic alterations resulting from coronary atherosclerosis the reader is referred to Bork,[11] Jores,[100] Wolkoff,[39] Leary,[1] Glomset.[7, 48]

MICROSCOPIC APPEARANCE OF CORONARY ATHEROSCLEROSIS

The primary and predominant lesions occur in the intima *There is uncertainty as to the very earliest lesions* According to Klotz,[117] Leary[1??, 1 3] and others the initial change is the presence of lipid-containing macrophages (foam cells) in the subendothelial layer of the intima Shortly thereafter, if not simultaneously, there are deposits of lipoidal material in the ground substance of the intima as well as in the large mononuclear foam cells The initial foci of lipid within and outside the *macrophages coalesce to form lipid rich* intimal plaques Vacuolar degeneration and swelling of the metachromatic ground substance and collagen framework of the intima are also observed in early lesions According to Aschoff[11] and others[144] these changes, including the deposition of mucoid ground substance the formation of fibroblasts and collagen and the proliferation of elastic tissue, are primary and the deposition of *lipids secondary*

Subsequently thickening of the intima results from a proliferation of reactive or reparative connective tissue, from increased deposition of lipids within and outside of foam cells the formation of new capillaries, calcification and rarely bone formation The internal elastic lamella may be displaced and fragmented Sometimes it disappears while newly formed delicate elastic fibrils arise in the atherosclerotic plaque

The changes which follow the initial intimal lipoidosis and degeneration appear to represent attempts at repair or the consequences of disturbances in nutrition Normally the intima receives most or all of its nutrition by imbibition from the arterial lumen The *deposition of lipid and the formation of new* collagen to repair the damaged intima result in significant thickening of this layer of the artery In consequence, imbibition from the lumen even when supplemented by that from the adventitial vasa vasorum, is inadequate to nourish all portions of the thickened intima *Newly formed capillaries arise in the intima,* occasionally from the lumen, but more frequently from the vasa vasorum[8, ?] From this viewpoint the intimal capillaries represent a granulation tissue type of reparative structure designed to compensate for local nutritional deficiencies

Subsequent changes appear to be determined by the ability of these new nutritive channels to keep pace with increasing lipid and other degenerative changes and fibrosis A deficiency in nutrition results in necrosis of *the atherosclerotic plaque The latter, which is* filled with lipid becomes softened and forms the so-called atheroma, atheromatous abscess or cyst, which is composed of necrotic and degenerative tissue including cellular detritus, cholesterol esters and other lipids The atheromatous plaque often causes a unilateral thickening of the vessel wall and an eccentric lumen The atheroma may extend to the surface and rupture through the intima *emptying its contents into the lumen and* producing an atheromatous ulcer Calcium is deposited around the atheromatous focus as well as in the thickened fibrous hyalinized areas of the intima Large calcified plaques may result and occasionally bone is deposited in or replaces calcified areas Rupture of the intimal capillaries results in *localized hemorrhages* which may either advance the atherosclerotic process by increasing the circulatory *insufficiency or, more important may result* in acute coronary occlusion (p 500) Fibrinoid intimal masses often found in the region of atherosclerotic plaques may represent compressed and hyalinized elements of the blood due to such hemorrhage[11]

Changes in the media are much less prominent *and consist of atrophy of the muscular* and elastic elements This is probably the result of compression by the thickened intima The atrophic changes produce thinning and sometimes almost complete disappearance of the medial layer of the artery Fibrosis and hyalinization of the media are not uncommon in the region of the atherosclerotic plaque Occasionally lipoid material and calcium may be deposited in the media as well as in the intima, *especially when the frayed, fragmented* intimal elastic membrane is ruptured and permits the invasion of the media by the atheromatous material Sometimes capillaries may be seen extending from the adventitia through the media to the basal layers of the intima

The adventitial changes are less striking but frequently irregular patches of fibrosis and focal collections of lymphocytes simulate inflammatory lesions[64]

MACROSCOPIC PATHOLOGY

Mild lesions are represented by superficial *yellowish lipoid flecks, streaks or nodules on* the intimal surface or by small white patches

of fibrous thickening More advanced lesions cause pronounced thickening and rigidity of the vascular wall and thick lipoid, fibrous or calcified intimal plaques which protrude into and encroach on the lumen Atherosclerosis of the coronary arteries usually involves the epicardial branches without extending into the branches penetrating the myocardium The most advanced lesion in the epicardial vessel is on the surface nearest the muscle [48] Extreme degrees of narrowing may result, but evaluation of coronary stenosis at necropsy examination should make allowance for postmortem collapse [107] Extensive calcification of the coronary artery wall may produce a pipe-stem consistency Revascularization of the atheromatous plaques intimal hemorrhages and extension of intimal necrosis to the surface causing ulceration are among the common occurrences Blood platelet thrombi may be deposited in such atheromatous ulcers Zak and Elias [44] found evidence that extrusion of the contents of atheromata with resulting embolism to more distal positions of the coronary arteries is more common than has been suspected

The most serious complication of coronary atherosclerosis is thrombotic occlusion (for pathology see p 499) In addition atherosclerotic aneurysm and rupture occur rarely [183] Rupture of such an aneurysm may cause hemopericardium and fatal cardiac tamponade [166]

The Heart in Coronary Atherosclerosis

As a rule uncomplicated coronary atherosclerosis is unaccompanied by significant cardiac lesions unless the degree of narrowing of the vessels seriously impairs the blood supply to the myocardium In most instances actual occlusion of the vessel accounts for gross myocardial change (for pathology of the heart in coronary occlusion see p 501) Under certain circumstances prolonged coronary insufficiency can occur without coronary occlusion and the resultant myocardial anoxia may be followed by focal or extensive areas of subendocardial myocardial necrosis of the left ventricle and papillary muscles (p 505)

Frequently severe coronary atherosclerosis with narrowing but without occlusion is accompanied by fine diffuse fibrosis of the heart muscle confined essentially to the left ventricle and papillary muscles Of 37 cases of severe coronary atherosclerosis without occlusion Clawson[7] observed severe myocardial fibrosis of irregular distribution in 18 slight fibrosis in 17 and none in 2 These lesions are interpreted as fibrous replacement of myocardial fibers which atrophied or degenerated and disappeared as a result of ischemia The fibrosis is not a result of inflammation and therefore the term myocarditis is inappropriate Somewhat similar diffuse fibrosis may be observed as a result of longstanding ischemia in calcific aortic stenosis (p 701) and in cases of malignant hypertension

The heart is of normal size or slightly hypertrophied in uncomplicated coronary atherosclerosis Moderate left ventricular hypertrophy is frequently present because of an associated hypertension When coronary atherosclerosis with or without occlusion results in congestive heart failure pronounced dilatation and hypertrophy of the heart develop

PATHOLOGIC PHYSIOLOGY

Physiologic disturbances of the heart and clinical manifestations result when the atherosclerotic process seriously impairs the coronary blood supply to the myocardium This may occur in the following ways

(1) Atherosclerotic occlusion of an artery may lead to infarction of a portion of myocardium This is discussed below (p 497)

(2) Occlusion of an artery may result in chronic potential anoxia of a portion of myocardium The collateral circulation prevents infarction (see under angina pectoris p 455)

(3) Multiple coronary occlusions and myocardial infarctions heal but so impair cardiac structure and function as to cause heart failure

(4) Coronary atherosclerosis and narrowing insufficient in themselves to produce symptoms may cause coronary insufficiency and cardiac decompensation in a preexisting enlarged rheumatic syphilitic or hypertensive heart

(5) Extreme atherosclerotic coronary narrowing without occlusion may cause clinical evidence of coronary insufficiency when the demands of the heart muscle increase

(6) Atherosclerotic rigidity of the coronary vessels may impair their ability to adjust in caliber to changing cardiac demands for blood This is theoretical

It will be observed that atherosclerotic heart disease in the clinical sense results usually from recent or old coronary artery

occlusions and to a lesser extent from extreme coronary narrowing without occlusion Lesser degrees of interference with blood flow are rarely of physiologic or clinical significance

CLINICAL FEATURES

The clinical features of coronary heart disease may be classified into a variety of syndromes one or more of which may occur in the same patient at the same or different times during the course of the disease

1 Angina pectoris or cardiac pain
2 Acute coronary occlusion and myocardial infarction
3 Left-sided heart failure including cardiac asthma
4 Combined left and right sided heart failure
5 Heart block and other disturbances in conduction and rhythm
6 Gastrointestinal and substitution symptoms
7 Sudden death
8 Latent or asymptomatic cases

Angina Pectoris and Coronary Occlusion

Angina pectoris and acute coronary occlusion and myocardial infarction are the most frequent and important manifestations of coronary heart disease For this reason special chapters are devoted to their discussion (see Chapters 17 to 21)

Heart Failure

Manifestations of congestive heart failure (Chapter 7) may emerge after a previous history of angina pectoris or myocardial infarction or they may appear gradually or suddenly as the initial symptoms of coronary heart disease Heart failure may be viewed as the result of progressive coronary narrowing and insufficiency or of repeated myocardial infarcts When heart failure is the initial manifestation it is assumed either that progressive cardiac damage occurred without preceding acute localized areas of myocardial anoxia or infarction or that such episodes were clinically asymptomatic or unrecognized Frequently acute left ventricular failure (pulmonary edema) develops concomitantly with a clinical episode of acute myocardial infarction, or left- and right sided heart failure develops more or less rapidly after recovery from the attack

Left sided heart failure develops earlier and more commonly because the coronary arteries supplying the left ventricle are most affected by atherosclerosis infarcts are almost exclusively in the left ventricle and because the left ventricle performs more work and has a greater muscle mass and is therefore more susceptible to ischemia Frequently associated hypertension also contributes to the development of left ventricular failure in cases of atherosclerotic heart disease

Dyspnea on exertion or nocturnal attacks of cardiac asthma are the cardinal symptoms Frequently patients with coronary heart disease suffer from angina pectoris as well as heart failure, therefore cardiac pain and exertional dyspnea or nocturnal dyspnea may occur in the same patient Restriction of activity because of the pain may obscure exertional dyspnea Weakness is a frequent complaint Orthopnea and cough due to pulmonary congestion are common symptoms with advanced left-sided heart failure I have several times observed intractable cough as the dominant symptom of atherosclerotic heart disease Right sided heart failure, including peripheral edema hepatic enlargement and systemic venous engorgement often follows and is combined with evidence of left ventricular failure

Cardiac Arrhythmias

Heart block is an uncommon manifestation of coronary atherosclerosis even though the latter with or without occlusion is its most frequent cause Rarely heart block is the first or only evidence of an acute coronary occlusion (p 539) The heart block may be asymptomatic it may give rise to palpitation or precordial discomfort or it may be associated with Adams-Stokes syndrome (p 540) (For a detailed discussion of heart block see p 384)

Coronary heart disease is characterized by the frequency of disturbance in mechanism, i e in rate rhythm or rhythmicity, as well as in mechanical function as a pump Hence ventricular standstill and fibrillation are common at some time in the course of the disease and are often responsible for sudden death Frequently there is a discrepancy between the amount of anatomic disease with consequent symptoms of myocardial ischemia or heart failure and the disturbance in cardiac mechanism Unfortunately, disturbances in cardiac mechanism with a fatal outcome occur frequently when the extent of myocardial infarction or fibrosis would not have caused serious chronic cardiac disability

Bundle branch and intraventricular block (p 395) are more common and may be associated with atrioventricular block The former conduction disturbances do not produce symptoms, but angina pectoris or congestive heart failure is often present Not infrequently the finding of bundle branch or intraventricular block in asymptomatic persons is the sole clue to the presence of atherosclerotic heart disease But other causes of intraventricular block must be considered (e g calcific aortic stenosis gumma diphtheria rheumatic fever tumors or cysts drugs)

Atrial fibrillation occurs commonly in advanced cases of atherosclerotic heart disease with congestive heart failure The occurrence of atrial fibrillation may be the first evidence which leads to the discovery of previously unrecognized atherosclerotic heart disease Premature beats are common but not characteristic of this disease

Digestive disturbances may be prominent symptoms of coronary heart disease The resemblance of acute myocardial infarction to an acute attack of indigestion is well known Gaseous eructations may accompany or follow paroxysms of angina pectoris The development of digestive disturbances predominantly on exertion should suggest coronary insufficiency Postprandial abdominal fullness meteorism belching and flatulence may be due to chronic cholecystitis or functional digestive disturbances but may also result from coronary heart disease Digestive disturbances in this type of heart disease may also be due to heart failure (p 155) or to overdosage with digitalis (p 264)

Sudden death (p 316) is due most commonly to coronary heart disease if accidents and poisonings are excluded It is a common termination in cases of angina pectoris and is often associated with acute coronary occlusion (p 513) But sudden death may complicate coronary heart disease without the occurrence of an acute occlusion[378] Coronary atherosclerosis with pronounced coronary narrowing but no occlusion or infarction was observed by French and Dock[59] in many cases of sudden death in young soldiers Under the heading of acute fatal coronary insufficiency Levy and Bruenn[1 6] described a series of hospitalized patients with coronary heart disease who died suddenly and who at postmortem examination presented coronary atherosclerosis but no fresh occlusion or other anatomic lesion to explain the immediate cause of death They observed an 11 8 per cent incidence of sudden death in a group of patients with coronary sclerosis without thrombosis as compared with 33 3 per cent in a similar group with coronary thrombosis Sudden death occurred in 27 5 per cent of those patients who presented a history of cardiac pain and in 9 1 per cent of those without such pain Sudden death in coronary heart disease is usually attributed to ventricular fibrillation cardiac standstill acute massive pulmonary embolism or cardiac rupture following acute myocardial infarction

Finally coronary heart disease may be asymptomatic for long periods of time its presence being indicated by a past history of angina pectoris or myocardial infarction or by electrocardiographic abnormalities (see below)

DIAGNOSIS OF CORONARY (ATHEROSCLEROTIC) HEART DISEASE

The diagnosis of coronary heart disease is based most often on a past or present history of acute myocardial infarction or of angina pectoris Other causes of angina pectoris such as calcific aortic stenosis (p 700) syphilitic ostial stenosis (p 896) or extreme anemia are usually relatively easy to distinguish

In the absence of myocardial infarction or angina pectoris the diagnosis of coronary heart disease is always uncertain but may be presumed if manifestations of congestive heart failure especially cardiac asthma or pulmonary edema appear in patients past 45 years of age who present no other apparent cause for these symptoms Electrocardiographic changes (see below) suggestive of recent or old myocardial infarction lend support to the diagnosis Attacks of Adams Stokes syndrome are usually indicative of atherosclerotic heart disease

Electrocardiographic Changes

Electrocardiographic abnormalities may be absent in one quarter to one half of the cases of coronary heart disease especially in those characterized only by angina pectoris Sometimes a presumptive diagnosis of coronary heart disease is justifiable on the basis of routine electrocardiographic findings The distinctive electrocardiographic abnormalities of acute myocardial infarction (p 521) are of course diagnostic Healed infarction may be disclosed by persistent M or W shaped QRS complexes in lead I or II by the

presence of a large Q and an inverted T wave in lead I or by similar findings in leads II and III, or by absence of R waves and inverted T waves in precordial leads over the left ventricle.

T wave inversions often denote myocardial impairment due to coronary atherosclerosis but may be due to a variety of other causes[1,4] which can often be excluded. S-T interval deviations may be associated. Inversion of T_1 and especially of T_1 and T_2 are much more significant than isolated inversion of T_3. *Inversion of the T wave in the precordial* leads occurs commonly in coronary heart disease and is usually more striking than in the standard leads.[72] But T wave inversions may result from positional deviation of the electrical axis of the heart or from cardiac hypertrophy due to causes other than coronary atherosclerosis. Inversion of T_3 is common in obese individuals or as a result of *other factors which elevate the diaphragm or* produce a transverse position of the heart. Occasionally T_2 as well as T_3 may become inverted as a result of respiratory or postural changes. Inversion of T_1 with depression of ST_1 and left axis deviation is common with severe hypertension[13] and may not necessarily denote coronary heart disease. Digitalis causes pronounced T wave inversions and S-T depressions which are often distinctive (p. 269). T wave inversions due to pericarditis, a variety of acute infections or toxic or nutritional disturbances can usually be differentiated by the clinical history. S-T interval depressions and/or lowering or inversion of T waves appearing after an exercise or anoxemia test are strongly confirmative of coronary heart disease (coronary insufficiency) *when there is a clinical suspicion of that condition or the clinical features are atypical.* RS-T segment coving and frank T wave inversions in the mid- and left precordial leads may occur in anxious, tense individuals, especially Negroes, without other evidence of heart disease.[7,38] Such changes have been attributed to hyperventilation or to vagal reflexes. The administration of the vagal blocking agent *Pro-Banthine results in prompt normaliza*tion of the electrocardiographic abnormalities.

Q waves may be indicative of coronary heart disease. Often they persist with or without T wave inversion, as the residua of a previous cardiac infarction. A large Q_3, often associated with a Q_2, may persist after infarction of the posterior wall of the left ventricle, but a Q wave is often present in lead III in normal individuals. According to Pardee[165] and Durant[50] *a Q_3 is significant of myocardial damage* only if the voltage of the Q wave is at least one-fourth as great as that of the tallest QRS complex in any standard lead and if a Q_2 of at least 1 mm. is also present. Durant[50] found that the significance of a Q_3 as an indicator of coronary heart disease was enhanced if: (a) Q_3 was at least half as large as the tallest R, (b) Q_2 was at least one quarter as large as R_2 *and (c) there was no right axis deviation.* A Q_3 prolonged to more than 0.04 second is suggestive of coronary heart disease. Differentiation of normal from abnormal Q waves in lead III has been facilitated by the use of an augmented unipolar left leg lead.[184]

Both with respect to T and ST abnormalities and to the finding of Q waves, their significance in the diagnosis of coronary heart *disease increases if they disclose progressive* change in repeated observations over a period of months or years.[26]

Conduction disturbances are often suggestive of coronary heart disease when they are observed in middle-aged or older individuals and if rheumatic heart disease, syphilitic heart disease, congenital cardiovascular disease, diphtheria and other infections and drugs *such as digitalis or quinidine can be excluded* as etiologic factors. Such exclusion is often possible on the basis of the history, physical examinations and laboratory tests. Partial or complete heart block may be observed in patients with old and often unrecognized coronary occlusions or in cases of severe but nonocclusive coronary atherosclerosis. Bundle branch block, especially of the left bundle, and intraventricular conduction *defects,* characterized by widening of the QRS interval to 0.12 second or more and by slurring and notching of the QRS waves, are usually diagnostic of coronary heart disease. But rheumatic fever, diphtheria, congenital lesions, quinidine and the Wolff-Parkinson-White syndrome must be excluded. Low voltage, with or without slurring of the QRS complexes *in leads I and II, often with low or in*verted T waves, is suggestive of coronary heart disease if myxedema, constrictive pericarditis and pericardial effusion can be excluded. QRS complexes which are of low voltage, slurred and notched only in lead *III* or in right precordial leads are usually insig

nificant But notching of the R wave especially near the apex in leads I and II is indicative of myocardial damage usually due to coronary athero clerosis

Roentgenologic examination may help in the diagnosis Occasionally an enlarged cardiac silhouette is the first clue to the presence of unrecognized coronary heart disease which is then confirmed by a careful history or electrocardiographic examination Absence or reversal of left ventricular pulsation discovered by fluoroscopy may similarly suggest or add support to a diagnosis of coronary heart disease with old infarction and possible ventricular aneurysm The roentgenogram may reveal calcification of the coronary arteries which appear as linear and segmental streaks in curves corresponding to the course of the vessels[36] Calcification denotes coronary atherosclerosis but not necessarily clinical coronary heart disease

Summary of Diagnostic Features

1 Clinical or electrocardiographic evidence of a recent or past attack of myocardial infarction warrants a diagnosis of coronary heart disease

2 Angina pectoris usually denotes coronary heart disease but less common causes of this syndrome must be excluded

3 Electrocardiographic abnormalities including T wave inversions and ST deviations the presence of Q waves and atrioventricular and intraventricular conduction disturbances often permit a presumptive diagnosis of coronary heart disease if due regard is given to the age and clinical history of the patient and if other causes of such electrocardiographic changes can be reasonably excluded

4 Cardiac enlargement and congestive heart failure in middle aged or elderly subjects may suggest the presence of coronary heart disease but these abnormalities should provoke a careful review of the history and findings on physical and electrocardiographic examination in an effort to confirm the diagnosis or discover other etiologic factors

Certain misconceptions regarding the diagnosis of coronary heart disease should be dispelled Heart failure or other abnormal cardiac findings are not necessarily due to coronary heart disease merely because the patient is past 50 or past 60 years of age neither does youth exclude this diagnosis The finding of arteriosclerotic radial arteries or of atherosclerosis of the aorta lower extremities or the retinal vessels does not denote that coronary heart disease is also present Coronary (atherosclerotic) heart disease is not excluded because of the absence of physical signs in the heart or because of a normal cardiac size or a normal electrocardiogram

PROGNOSIS

The course and prognosis of coronary heart diseases has been studied best in connection with its most specific manifestations viz cardiac infarction angina pectoris heart failure bundle branch block and is discussed in detail under these individual headings

TREATMENT

The treatment of coronary heart disease is essentially that of its specific manifestations such as heart failure (p 234) myocardial infarction (p 562) angina pectoris (p 470) or the various arrhythmias To avoid repetition I refer the reader to these headings

Theoretically it would be desirable to direct treatment against the basic cause namely atherosclerosis Most of the measures designed to prevent retard or diminish human coronary atherosclerosis are presumed to act by modifying cholesterol metabolism or diminishing cholesterol absorption thereby reducing the serum cholesterol Or agents have been used to stabilize cholesterol solubility in the blood thereby diminishing its deposition in the arterial intima The therapeutic rationale assumes that an abnormal level of serum cholesterol or of lipoproteins containing the cholesterol or an abnormal state of serum lipid solubility is the major factor in the development of atherosclerosis Among the therapeutic measures which have been considered for their possible effect in reducing or stabilizing serum cholesterol or otherwise opposing atherosclerosis are (1) weight reduction by low calorie diet (2) low fat and/or low cholesterol diets (3) plant sterols sitosterol or specific vegetable fats dihydrocholesterol and other cholesterol analogues (4) lipotropic agents heparin like substances (5) detergents (6) estrogens (7) iodides and thyroid extract

The efficacy of any of these measures with regard to the prevention or treatment of human coronary atherosclerosis is as yet unproven From the viewpoint of clinical practice there is *no acceptable specific treatment* of coronary atherosclerosis Many of the

recommended measures deserve and are undergoing further investigation. Unfortunately it is difficult to evaluate clinical therapeutic studies because there is no convenient accurate method of evaluating the presence, degree or progression of human coronary atherosclerosis. Furthermore because of the long duration and the clinical variation of the natural life history of coronary atherosclerosis, very large numbers of cases and very prolonged periods of observation are necessary. The following individual therapeutic measures are discussed not because they are recommended but because the problem of whether to prescribe them arises frequently in clinical practice.

1 Weight Reduction. Low Calorie Diet

There is more general agreement as to the desirability of weight reduction by a low calorie diet than as to any reduction in specific dietary factors such as cholesterol or fat. The prevalance of coronary atherosclerosis has been correlated with obesity and high caloric intake.[30, 1, 45] On the other hand coronary heart disease also occurs frequently in patients who are not overweight and epidemiologic studies have indicated that obesity occurs as commonly in Bantus or southern Italians who are relatively free of coronary atherosclerosis as among Americans or Swedes with a high incidence of coronary atherosclerotic heart disease. Walker and associates[1] reported that an average weight loss of 19 pounds in 39 subjects led to a reduction in total serum cholesterol and in the atherogenic S_f12–20, 21–35 and 35–100 classes of lipoproteins in most cases, but other observers found no reduction in serum cholesterol or other lipids following weight reduction.[143, 171] It should be reemphasized however that the level of serum cholesterol or lipoproteins has not been proved to be an accurate index of atherosclerosis and that a therapeutic measure may be beneficial for coronary atherosclerosis even when it does not modify the serum lipids.

Weight reduction should be recommended for all overweight patients with coronary heart disease. Clinical impressions and statistical data suggest that weight reduction is beneficial for well being and longevity; therefore it may be regarded as good therapeutic advice whether or not its benefit is due to a favorable effect in retarding or diminishing coronary atherosclerosis.

It is probably desirable to diminish obesity *gradually* by a moderate reduction in caloric intake especially of fats. During very rapid weight reduction utilization of the patient's own fat is tantamount to a high fat diet. I have been impressed by the number of instances in which an acute myocardial infarction followed a period of rapid weight reduction. As a rule these patients reduced their weight by following a very high animal protein low carbohydrate diet. The distribution of calories as well as the low calorie diet may be important when weight is being reduced to prevent or retard coronary atherosclerosis.

2 Low Cholesterol or Low Fat Diets

A low cholesterol diet has been recommended because of the evidence relating cholesterol feeding and hypercholesterolemia to atherosclerosis. Attention has been directed to the difficulty of reducing the serum cholesterol significantly and continuously in man by a low cholesterol intake (p 424) presumably because of endogenous cholesterol formation from 2-carbon fragments derived from carbohydrates, fats or proteins. Most of the so-called low cholesterol diets prescribed by physicians are incapable of modifying the serum cholesterol.

To reduce significantly serum cholesterol by diet requires not only a low cholesterol but particularly a very low fat diet not exceeding 20 gm daily.[110] Such a low cholesterol low fat diet is the rice-fruit diet of Kempner which is free of cholesterol and contains not more than 5 gm of fat. Kempner[108] reported an average reduction of 74 mg per 100 cc (27%) in hypercholesteremic and 15 mg per 100 cc (8%) in normocholesteremic patients on the rice diet and similar findings were reported by Starke.[207] Watkin et al[224] reported that in 41 patients with essential hypertension in the second month of treatment with the rice diet there was a mean decline of 40 mg per 100 cc (17%) in serum total cholesterol, due chiefly to a reduction in the cholesterol ester fraction. But in 45 per cent of the cases there was either no significant decrease in serum cholesterol or the early decline was not sustained. Gofman and his associates[76] reported that very low cholesterol diets reduce the concentration of the S_f12–20 "atherogenic" lipoprotein aggregates. But Hatch and associates[83] reported no significant change in the S_f12–20 and a mean 100 per cent *increase* in the concentration of the S_f20 to

100 lipoprotein fractions on the rice diet with considerable variation among individual subjects The impalatability of such an extreme dietary regimen as the unmodified rice fruit diet imposes too great a hardship to permit prolonged use by the vast majority of patients In view of the inconstant and relatively small and frequently transient reduction in serum cholesterol induced by such a low cholesterol diet and the unproven benefit in preventing or reversing coronary atherosclerosis the prescription of such a low cholesterol diet cannot be regarded as warranted at the present time

Of even greater significance is the evidence that the control of serum lipid levels and the geographic or ethnic distribution of human coronary atherosclerosis is related to the fat intake and not to that of cholesterol, or else that a low cholesterol diet is of benefit only when fats are also greatly restricted[116, 86] Direct evidence of the benefit of low cholesterol and low fat intake was reported by Morrison[119] Fifty patients recently recovered from a proven attack of acute myocardial infarction were placed on a low cholesterol low fat diet (20 to 25 gm daily) and observed for 8 years while 50 similar patients were maintained as controls on their ordinary diet The mortality rate was 76 per cent in the control group 44 per cent in the group on the low cholesterol diet All serum lipid fractions were reduced Attacks of angina pectoris decreased in severity and frequency and exercise tolerance increased in the group in low cholesterol intake However it is questionable whether a significant conclusion can be drawn from this study

A list of foods relatively rich in cholesterol stresses dairy products and raises the question of a possible causal relation between the increased intake of dairy products in countries with the highest incidence of coronary atherosclerosis (e g the United States Great Britain Denmark) The following foods are *cholesterol rich*

1 Whole milk cream cheese and cheese spreads butter ice cream
2 Egg yolk
3 Liver brains heart, kidney sweetbreads fish roe
4 Animal fats such as fatty meats pork bacon lard fatty fish (salmon mackerel, tuna whitefish)
5 Oysters shrimps brewers yeast
6 Salad dressings containing olive oil rich gravies olives nuts avocados
7 Cream soups
8 Hot breads pancakes waffles many puddings coffee cakes muffins doughnuts
9 Desserts made with cream or egg yolks pies frozen creams

Even neutral fats are undesirable in low cholesterol diets because they aid the absorption of cholesterol In this respect vegetable fats may act like animal fats

A *cholesterol poor diet* permits

1 Skimmed milk and buttermilk without fat
2 Whites of egg
3 Lean meats and lean fish (in small quantities)
4 Fat-free broth bouillon or soups
5 Cooked and raw vegetables
6 Fruits
7 Cooked or dry cereals
8 Salads with salad dressings of mineral oil lemon juice vinegar ketchup spices
9 Tea coffee tomato juice sugar jellies
10 Breads with oleomargarine potatoes according to desired caloric and fat intake

Chocolate lard margarine hydrogenated fats and salad oils are high in fat but not in cholesterol It should be stressed that present evidence does not clearly indicate whether all fats or only animal fats should be curtailed in the diet of the patient with clinical coronary disease Excessive caloric intake should be avoided and fats should provide no more than 20 to 25 per cent of total calories

3 *Plant Sterols*

The plant sterol sitosterol was found to lower serum cholesterol in chicks[169] and man[176] and to decrease the incidence of atherosclerosis in cholesterol fed rabbits[174] and chicks[169] Sitosterol is presumed to act by interfering with the absorption of dietary cholesterol and cholesterol excreted by the liver into the gastrointestinal tract perhaps by competing for esterification[93, ...] Best and associates[19] observed a sustained reduction of serum total cholesterol cholesterol lipid phosphorus ratio and so-called atherogenic Sf 10-100 lipoprotein aggregates when 20 to 25 gm beta sitosterol was administered daily in divided doses before meals to 14 subjects on free diets Similarly Farquhar and Smith[55] observed that the administration of 9 to 18

gm daily of beta sitosterol to 15 normotensive, non-diabetic men who had previous myocardial infarction resulted in a significant fall in serum cholesterol total lipid and beta lipoprotein lipid with insignificant change in alpha lipoprotein Whether this has any practical application to the control of coronary atherosclerosis is unproven at this time More recently Ahrens and associates[4] fed a variety of single well defined fats of plant and animal origin to 3 normocholesteremic and 4 hypercholesteremic patients A reduction in serum lipids was most striking during the intake of corn oil as compared with olive lard or coconut oil They concluded that the reduction in lipid levels following feeding of plant fats was dependent on the specific fat which was fed and not on the decreased intake of cholesterol The effect was not due to the sitosterol content of the corn oil

In addition to the sitosterols and corn oil other substances have been administered in an effort to reduce the serum cholesterol by interfering with cholesterol absorption e g , dihydrocholesterol the cholesterol analogue cholesteryl chloride, and cholesterol free lipid poor brain extracts There is inadequate justification for the clinical administration of any of the substances listed under this heading

4 Lipotropic Agents

There is little basis for the therapeutic use of the lipotropic agents choline, methionine and inositol Yet they are widely prescribed in clinical practice for the prevention and treatment of coronary heart disease These agents have been shown to be effective in preventing or reversing the fatty degeneration of the liver associated with certain nutritional deficiencies, but experimental evidence regarding the effect of lipotropic agents on serum lipids and atherosclerosis is inconclusive and controversial[152 200 41 39 22] Because the lipotropic substances constitute an important part of the phospholipids, it was thought that they might aid in stabilizing the colloid dispersion of plasma cholesterol, but there is no direct evidence that they accomplish this when given orally A depression of serum cholesterol has been reported in patients with hypercholesterolemia who had survived a myocardial infarct and were given inositol for eight weeks[57] Morrison[158] has claimed that lipotropic agents elevated the serum phospholipids and thus reduced the serum cholesterol phospholipid ratio in patients with coronary heart disease provided that they adhered to a low cholesterol, low fat intake (20 to 25 gm fat daily) and that large doses of the lipotropic agents were given for at least six months Despite these and similar claims which are based on unconvincing clinical observations critical analysis of available studies indicates that lipotropic agents are ineffective in the treatment of coronary atherosclerosis[101]

5 Heparin and Heparin-Related Substances

The clearing effect of injected heparin on lipemic blood plasma and its reported beneficial effect on blood lipoproteins and experimental atherosclerosis (p 422) suggested its clinical use in coronary heart disease Its reported beneficial effect on angina pectoris will be discussed (p 482) At the present time there is insufficient evidence to justify the use of heparin for the treatment of coronary atherosclerosis even though Engelberg et al[65] reported that the subcutaneous administration of 200 mg of heparin twice weekly to 105 patients with a previous myocardial infarction was followed by only 4 cardiovascular deaths over a two year period, whereas there were 21 deaths among a control group of 117 patients with previous myocardial infarction who did not receive heparin

6 Detergents

Despite the reports of the beneficial influence of surface-active detergents on blood lipids and experimental atherosclerosis (p 422) there is no evidence to justify their clinical use to control coronary atherosclerosis

7 Estrogens

The evidence relating the sex hormones to experimental and human atherosclerosis has been presented (pp 427-8) The presumably favorable influence of estrogens on the serum lipids and lipoproteins of survivors of myocardial infarction[15] was effected by large doses which were accompanied by usually intolerable side effects These included swelling of the breasts, loss of libido, impotence, depression and irritability The administration of androgens to neutralize these side effects resulted also in an abolition of the desired estrogen effects on serum lipids The use of estrogens for the specific treatment of coronary atherosclerosis in clinical practice is unwarranted at present

6 Thyroid Extract and Iodides

The relationships between thyroid hormones and blood cholesterol and experimental atherosclerosis have been presented (p 428). These relationships have suggested the possible value of administering thyroid extract to patients with clinical evidence of coronary atherosclerosis. Although thyroid extract has been administered empirically, its value has not been established.

Similarly iodides have been administered empirically without proof of clinical benefit, based largely on the inhibitory effect of iodides on experimentally induced atherosclerosis in cholesterol fed animals.

OTHER DISEASES OF THE CORONARY ARTERIES

Disease of the coronary arteries may be due to a variety of other causes as well as to atherosclerosis. The principal causes include

1. Atherosclerosis
2. Syphilis
3. Rheumatic fever
4. Other infections
5. Periarteritis nodosa
6. Embolism
7. Aneurysm
8. Trauma
9. Congenital abnormalities
10. Thromboangiitis obliterans
11. Medial calcification

For the most part these conditions produce only pathologic anatomic lesions which may be entirely asymptomatic. Clinical manifestations of heart disease may result when these lesions interfere significantly with the vascular supply of a portion of the myocardium or when rupture of a coronary artery and consequent hemorrhage are followed by hemopericardium and cardiac tamponade. Thus a clear distinction must be made between coronary artery disease representing asymptomatic anatomic lesions and clinical forms of heart disease due to coronary artery disease and its resulting myocardial damage.

1 Coronary atherosclerosis has been discussed.

2 Syphilis of the coronary arteries is discussed in the chapter on cardiovascular syphilis (p 894).

3 Rheumatic fever is associated frequently with lesions of the coronary arteries but these are almost always microscopic and not responsible for clinical findings (p 819).

4 Other Infections

Inflammatory changes of the coronary arteries with granular degeneration, cellular infiltration, atrophy and fibrosis were noted by Wiesel [7] and by Wiesner [3] in a variety of infectious diseases, especially diphtheria and scarlet fever, but also typhoid fever, influenza, pneumonia and pyogenic infections. As a rule the lesions were visible only microscopically and affected the media predominantly. But they occasionally extended to the intima where they were grossly visible as minute slightly elevated yellow plaques. The significance and frequency of these lesions were minimized by Scharpff [133].

In cases of *typhus fever* the capillaries and arterioles of the heart, as well as of other organs, suffer from severe necrosis and thrombosis [84] but the larger coronary arteries are not significantly affected (p 915).

Destructive inflammatory changes in the coronary arteries occasionally result from general infections with bacteremia, especially in cases of *bacterial endocarditis* (p 868). Bacterial infection of the wall may cause a mycotic aneurysm. Minute infarcts due to bacterial emboli occur in a high percentage of cases [30].

Tuberculous arteritis involving the small coronary artery branches and arterioles was noted by Gouley and associates[71] in 5 of their 6 cases of myocardial tuberculosis. Most often there was an intimal thickening with little or no cellular proliferation. This led to almost complete obliteration of some small vessels. Occasionally there were intimal tubercles. In one case there was extensive destruction of the large coronary arteries and veins by direct invasion of tuberculous inflammatory tissue.

The lesions of the coronary arteries associated with infectious diseases other than syphilis rarely lead to coronary occlusion [151, 18] but in a case of Salmonella choleraesuis infection[34] an arteritis with thrombosis caused occlusion of the left anterior descending coronary artery with infarction of the left ventricle. The electrocardiogram showed the classic pattern of anterior wall infarction (p 525). The coronary arteries were said to be involved in one quarter of the cases of brucellosis studied by Manchester [17].

5 Periarteritis (Polyarteritis) Nodosa (Necrotizing Arteritis)

The coronary arteries are affected in 60 to 70 per cent of that motley group of cases

known as periarteritis nodosa [1,7,81,155] They were involved in 11 out of 15 cases reported by Spiegel [158] The lesions are characterized by inflammation, necrosis and eosinophilic degeneration of the media and adventitia, and a periarterial inflammatory reaction Often the necrotic wall yields and gives rise to nodular aneurysms The term periarteritis nodosa as used by Kussmaul and Maier[119] may be applied properly only to *those cases in which there are grossly visible* circumscribed nodular thickenings of the arteries, but in recent years cases have been included in which there is merely a microscopic necrotizing arteritis and periarteritis (polyarteritis nodosa) Healing may occur with fibrosis of the vessel wall [20]

Often the inflammatory lesion extends to the intima and may occasionally be complicated by thrombosis Thrombosis of a large coronary vessel may result in myocardial infarction and a clinical picture resembling that due to acute atherosclerotic coronary occlusion [80] I have seen one case in which there was massive infarction of the right atrium But myocardial infarction is rare either because the occluded vessel is small or because the occlusion evolves so gradually that an adequate collateral circulation develops In such cases there may be no clinical *symptoms or only those of mild coronary in*sufficiency, the electrocardiogram may disclose T wave inversions [1,7] Hypertension eventually develops in most cases of periarteritis nodosa and may account for cardiac enlargement and electrocardiographic evidence of left ventricular strain Congestive heart failure is a common terminal event [155] When there are gross aneurysms due to necrotizing arteritis, there are usually no clinical manifestations Occasionally an aneurysm ruptures and results in hemopericardium which may be fatal [194] In one case which I observed this complication was overshadowed by an associated perirenal hematoma and uremia In 4 cases which I reported with Gross [60] the lesions of necrotizing arteritis were accompanied by typical endo myo-pericardial lesions of acute rheumatic fever A granulomatous coronary arteritis has been reported in association with temporal arteritis [35,150] In one case the coronary arteritis was associated with myocardial infarction

6 Coronary Embolism

Coronary embolism is said to be relatively rare [187] Hamman[86] collected 30 reported cases of embolic occlusion of large coronary branches and added 10 additional ones from the pathologic records of the Johns Hopkins Hospital These undoubtedly represent a small fraction of the actual cases which are unreported in medical literature Moragues et al [146] reviewed the literature up to 1950 The following are the usual varieties of coronary embolism

(a) Fragments of valve vegetation usually bacterial
(b) Blood platelet thrombus
(c) Fat embolism
(d) Air (gas) embolism

(a) The most commonly recognized type of coronary embolism is that associated with subacute or acute bacterial endocarditis Almost 50 per cent of the cases studied by Hamman[86] fell into this group Sudden or even instantaneous death usually occurs if the embolus occludes a major artery or the coronary ostium but sometimes the survival period is long enough for the formation of a myocardial infarct bland or septic

In the first case of clinically diagnosed acute coronary occlusion recorded by Hammer[87] in 1878, the occlusion was probably due to bacterial embolism of the coronary artery *arising in bacterial vegetations of the aortic* valve and sinus of Valsalva In this case diagnosis was possible because the patient lived for 10 hours after the occlusion Cheng et al [30] reported a proven case of coronary embolism diagnosed during life, in which the source of the embolism was a left atrial thrombus Rarely, when a coronary ostium is blocked by a polypoid vegetation, the occlusion may be intermittent with consequent intermittent attacks of cardiac pain

As a rule bacterial emboli are multiple and of minute size and reach the small coronary arterial branches or arterioles These produce numerous scattered small infarcts and focal inflammatory lesions, which may result in miliary abscesses (p 868) In occasional instances the bacterial emboli produce a small subepicardial myocardial abscess which may rupture into the pericardial cavity and give rise to a clinically recognizable pericarditis

(b) Next in frequency are coronary emboli consisting of bland blood thrombi These arise in thrombi deposited on aortic atherosclerotic plaques in the sinus of Valsalva or

immediately above it in mural thrombi on the left side of the heart in thrombi of the coronary arteries or in peripheral venous thrombi *The mural thrombi at the root of the* aorta may themselves block a coronary ostium or give rise to a major coronary embolus or both As a rule these thrombi are situated on atherosclerotic plaques but occasionally the underlying disease is due to syphilis as in the cases reported by Porter and Vaughan[174] In most of the reported cases the patients were males between 25 and 35 without clinical evidence of cardiac disease in whom death occurred suddenly

Mural thrombi on the left side of the heart may give rise to one or two emboli of major coronary branches or numerous emboli in small branches Myocardial infarction with its distinctive clinical picture is more frequent in the reported cases of embolism from mural thrombi than in coronary emboli from other sources Mural cardiac thrombi give rise to coronary *emboli much more rarely than to* cerebral or other visceral emboli the latter lesions usually determine the clinical picture When numerous small coronary emboli arise from mural thrombi they may produce multiple small infarcts with eventual extensive myocardial fibrosis and heart failure[86]

Peripheral venous thrombi give rise to coronary emboli only in the presence of a functionally patent foramen ovale since the embolus must cross from the venous to the arterial side of the circulation (paradoxical or crossed emboli) Pulmonary emboli are usually present at the same time The paradoxical emboli occlude the cerebral vessels much more often than the coronaries In instances of pulmonary suppuration or neoplasm emboli may arise from an affected pulmonary vein and cause cerebral abscess or metastasis *and perhaps very rarely coronary* embolism

Both the pathologic and clinical diagnosis of these forms of coronary embolism is difficult In the bacterial form the pathologic diagnosis can usually be made by demonstrating the source of the embolus in the valvular vegetations the similarity of structure of the embolus and bacterial vegetation and the relative normalcy of the coronary wall in the vicinity of the embolus The pathologic distinction between bland blood clot coronary emboli and thrombi is even more difficult

The clinical diagnosis is rarely made but may be suggested when death occurs instantaneously in cases of bacterial endocarditis *Sometimes however as in 3 cases re*ported by Garvin and Work[illegible] death occurs more or less gradually in 2 of them there was septic myocardial infarction 1 with distinctive clinical and electrocardiographic features

(c) Fat embolism of the coronary arterioles and capillaries either produces no clinical consequences or they are overshadowed by the manifestations of pulmonary fat emboli

(d) Air embolism of the small coronary vessels is also discussed later (p 967) It is uncertain whether the air emboli in the coronary vessels are responsible for any of the clinical manifestations the latter are usually due to emboli in the cerebral and pulmonary vessels[154]

Rarer forms of coronary emboli have been observed Thompson and Evans[15] reported a *case of solid tumor emboli in both coronary* arteries arising from a malignant teratoma of the testes which had entered a vein and crossed to the arterial side (paradoxical embolism) by way of a patent foramen ovale A mass of tumor tissue was seen projecting through the latter Merkel[129] reported the occlusion of a coronary artery by *Plasmodium falciparum* with resulting myocardial infarction

7 Coronary Aneurysms

Aneurysms of the coronary arteries are rare They are believed to be due to (a) periarteritis nodosa (necrotizing arteritis) (b) bacterial endocarditis or other generalized bacterial infections (c) atherosclerosis (d) congenital abnormality and in isolated instances to syphilis[161] trauma or rheumatic fever Dissecting aneurysm of the aorta may *extend into the coronary artery*[213] *or involve* its orifice[1,2] The most frequent cause of coronary aneurysm is probably periarteritis nodosa In these cases the aneurysms are often multiple and involve several branches

Excluding this type Packard and Wechsler[161] collected 29 cases from the literature and added one of their own subsequent reviews have brought the number up to 50[191, 216, 213] Most of these were congenital The aneurysms were three times as common in males as in females In the majority the aneurysm was single and involved the first inch of the left coronary artery However

aneurysms of the right coronary artery may have been more readily overlooked although several instances have been reported[76, 110]

Bacterial (mycotic) aneurysms arise either by bacterial embolization or more often by direct implantation of bacteria without embolic vegetation on the intima A secondary necrotizing or suppurative arteritis with weakening of the wall leads to aneurysm Such aneurysms are much more frequent in other vessels especially the cerebral

Atherosclerotic aneurysm of the coronary artery is the commonest form after the age of 50[111] Usually the aneurysm is associated with coronary sclerosis and narrowing Rukstinat[185] reported multiple atherosclerotic aneurysms of the right coronary artery

In 25 to 50 per cent of the last two groups (bacterial or atherosclerotic) the aneurysm ruptures and causes sudden death due to hemorrhage or hemopericardium and acute tamponade The rupture usually occurs first into the periaortic space and thence into the pericardial sac In the atherosclerotic cases associated coronary thrombosis and congestive heart failure are equally common causes of death

In one case of aneurysm of a coronary artery there was an arteriovenous fistula formed by a dilated atherosclerotic vessel communicating with the coronary artery and the right atrium[3]

8 Traumatic lesions of the coronary arteries are discussed in Chapter 45

9 Congenital coronary lesions **(p 791)**

10 *Thromboangiitis Obliterans*

Although the incidence of coronary disease and coronary occlusion in cases of thromboangiitis obliterans is said to be higher than is usual for the age group affected no indubitable case of thromboangiitis obliterans involving the coronary arteries has been reported However Saphir[■] in a review of 30 cases of thromboangiitis obliterans from the literature with special emphasis on the coronary changes reported 1 case in which he stated that the characteristic abnormalities seen in the extremities were also present in the coronary arteries These consisted of acute inflammation of all the layers of the vessels including veins as well as arteries miliary lesions with accumulations of polymorphonuclear leukocytes histiocytes and giant cells and *thrombus formation* *Lesions of coronary atherosclerosis* were found associated with these inflammatory changes

The patient, a 35 year old male after suffering for six years from the characteristic symptoms of intermittent claudication suddenly collapsed and died instantly Necropsy examination revealed multiple small cardiac infarcts and myocardial fibrosis in addition to the coronary lesions

11 *Medial calcification of the coronary arteries* with fibroplastic proliferation of the intima[210] also described as medial coronary sclerosis[■] apparently constitutes a distinct pathologic condition All the cases involve children less than twenty-seven months old There is an equal distribution between the sexes The media of the larger coronary arteries are extensively involved and the intimal proliferation may be sufficient to occlude the artery The cause is unknown but in some cases there were also severe renal lesions The lesions may be due to metastatic calcification as in cases of renal rickets hyperparathyroidism etc

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Chapter 17

ANGINA PECTORIS

Clinical Features, Etiology and Pathogenesis

The term angina pectoris was introduced by Heberden[43] (1768) to designate a very distinctive "disorder of the breast" attended with "a sense of strangling and anxiety." By using the word angina (strangling) it is clear that Heberden differentiated angina pectoris from multiple forms of chest pains of varied etiology, which were loosely assembled under the heading of *dolor pectoris*. Heberden described angina pectoris as a special disturbance in which the chest pain was of a peculiar modality and was often accompanied by psychic phenomena, most striking of which was a fear of impending death (angor animi). He noted that the pain generally occurred in paroxysms and that those afflicted with it were seized usually while walking, especially after a heavy meal, with an insupportable pain over the sternal region which rapidly vanished when the sufferer rested. There was no associated breathlessness. Those subject to angina pectoris were apparently well between attacks, but often died suddenly.

Angina pectoris refers to a symptom complex and not a disease.[37, 72] However, its occurrence strongly suggests the presence of one of several specific underlying cardiac diseases. It always indicates the same basic physiologic disturbance, probably myocardial anoxia, whatever the underlying disease.

Definition

Angina pectoris is a clinical syndrome characterized by paroxysmal attacks of a distinctive pain or oppression usually situated retrosternally, radiating commonly to the precordium and left upper extremity and occasionally to other adjacent areas, precipitated by effort and often also by other factors, relieved rapidly by rest or nitrites, and sometimes complicated by sudden death.

Certain elements may be atypical but the occurrence of the pain or pressure with effort is an essential element of the syndrome. Of course the pain of angina pectoris may occur at rest, but if it does not also occur with effort or cannot be reproduced by bodily exertion the diagnosis of angina pectoris may be questioned. By this definition angina pectoris applies only to a grave clinical syndrome resulting from paroxysmal relative inadequacy of blood supply to the heart. The pain of angina pectoris is distinguished from the more prolonged and usually more severe chest pain that results from acute myocardial infarction (see p. 509).

CHARACTERISTICS OF THE PAIN OF ANGINA PECTORIS

Location of the Pain

The primary site of the pain during a paroxysm of angina pectoris is usually at or behind the middle or upper third of the sternum. The term retrosternal is preferable to describe this location because substernal is misunderstood by many to designate the region below the xiphoid process. The pain is usually centered at the level of the third or fourth rib. Sometimes the primary site of the pain is more extensive and includes most of the precordium. Pains that are localized to a discrete area near the cardiac apex or to the left supracardiac region are rarely manifestations of angina pectoris. Rarely the pain [illegible] localized entirely to the right anterior chest but otherwise has all the characteristics of angina pectoris.[46]

Sometimes a patient experiences paroxysms of pain which occur under the same circumstances as angina pectoris but are not located in the anterior chest. The pain may affect the left scapular or interscapular region, the left wrist or other parts of the upper extremities, the epigastrium, and rarely even distant structures such as a carious tooth [illegible] an inflamed

gallbladder or the like While such pain cannot properly be termed angina pectoris its paroxysmal occurrence with general bodily effort and its prompt cessation with rest or nitroglycerin suggest that it is due to the same cause and may have the same serious implications including the possibility of sudden death

Radiation of the Pain

While the pain may be localized exclusively to its site of origin behind the sternum frequently especially when it is severe it tends to radiate to the neck jaw and upper extremities In its most characteristic form the pain radiates across the precordium to the left shoulder and upper arm but it frequently extends as far as the elbow the wrist or the fingers The pain may reach the shoulder and upper arm and then skip to the wrist or it may radiate to the wrist and fingers alone without involving any other portion of the extremity Sometimes the pain clearly follows the distribution of the ulnar nerve along the ventral and medial surface of the hand and fingers but it may also pursue a more diffuse and irregular course

When severe the pain may spread to both shoulders or even to both upper extremities Not infrequently it radiates to the right shoulder arm or wrist without involvement of the left (contralateral radiation—Libman[70]) The pain may extend to the clavicle lower neck or throat jaw and teeth especially on the left side Rarely it extends upward to the face head and scalp Occasionally the pain of angina pectoris starts in the sternal region and radiates exclusively or predominantly toward the left scapular region Rarely it radiates downward to the epigastrium or either hypochondrium distributions observed more commonly with the pain of an acute myocardial infarction Sometimes the pain starts in the left wrist arm or shoulder and radiates toward the sternum (inverse radiation—Libman[70])

Character of the Pain

The pain of angina pectoris may be mild severe or excruciating but whatever its intensity it usually has a special or even characteristic quality It was this quality which led Heberden[68] to designate it by the term angina meaning strangling Other descriptive adjectives which have been used are constricting pressing boring or expanding The pain or discomfort has also been described as a sense of a band or vise around the chest or a feeling of tightness The pain is usually dull not sharp sticking or knifelike and constant not throbbing But the pain may be described as burning or as a heartburn which has led to diagnostic confusion with peptic ulcer or hiatus hernia Sometimes patients say definitely that there is no pain but only an oppression or a choking or a sense of a weight over the breast bone or a vague indescribable distress

When there is a sensation of strangling or choking extending from the sternum to the throat the discomfort is sometimes confused with respiratory difficulty and may be erroneously interpreted as dyspnea The patient may speak of difficulty in breathing due to pectoral oppression but careful questioning will differentiate this from true dyspnea Often the pain so resembles that of gaseous distention behind the sternum that the patient tries to belch in order to obtain relief

The pain often has an insistent quality which compels the patient to remain as quiet as possible even to hold his breath and if he has been running or walking to come promptly to rest This is a special feature of the pain of angina pectoris which is not necessarily related to its severity for in some of the most intense types of pain such as that associated with ureteral colic the patient often moves or thrashes about in preference to remaining quiet Frequently the sensation in the arms wrist or hands is described as a numbness or weakness less commonly as tingling Occasionally weakness or numbness of the wrists or arms occurs without concomitant retrosternal or precordial pain in patients who at other times present the more complete picture of angina pectoris

The skin and subcutaneous tissue including the muscles of the areas affected by pain may be tender during the attack and even in the intervals between the paroxysms but this is unusual Vasomotor and trophic disturbances of these hyperalgesic areas such as blanching and blister formation resembling herpes zoster have been described[9] Instances of localized sweating of the shoulder or arm in patients with angina pectoris have been recorded[88] Occasionally there are evidences of reflex stimulation of the left cervical sympathetic nerve such as hyperhidrosis of the left side of the face and dilatation of the left

pupil[93] But none of these manifestations is a common or characteristic feature

Certain psychic features often accompany the pain of angina pectoris[42, 16] The fear of immediate impending death termed angor animi is well known Latham[61] described it as a sensation of approaching dissolution This is a pathognomonic diagnostic feature of the attack although it is often absent Frequently patients are embarrassed to admit this fear Careful interrogation however often discloses that this was the dominant feature of the attack and the reason for their seeking medical care The angor animi during the actual paroxysm of angina pectoris should not be confused with the more vague fears of death which torment patients who discover the nature of their disease and learn that it is often terminated by sudden death

Duration and Relief of the Attack

The attack of angina pectoris usually lasts only a few minutes Riseman and Brown[100] found that 97 per cent of attacks of angina pectoris precipitated by exertion actually lasted less than three minutes but that the patient usually greatly overestimated the duration Such attacks generally subside after a minute or two if the patient rests immediately when the pain begins On the other hand attacks which occur with the patient at rest often persist for five to fifteen minutes or up to a half hour but rarely longer A mild residual local soreness may not disappear for hours When severe pain lasts for more than a half hour the presence of an acute coronary occlusion should be strongly suspected

The attacks of angina pectoris vary greatly in frequency Many patients having learned the maximum activity in which they can indulge without pain avoid pain completely for long periods by restricting exercise below the critical point Some patients suffer a single paroxysm of pain early in the day usually on walking after which they are able to carry on normal activity without symptoms Others have only occasional seizures at intervals of days weeks or months the intervals depending to some extent on avoidance of the factors which excite their attacks Still other patients less fortunate experience numerous seizures each day, often without apparent cause, or after some slight activity or even after simple essential physiologic functions

OTHER SYMPTOMS AND SIGNS

There is usually no dyspnea or respiratory distress but the patient may complain of being unable to breathe or he may actually hold his breath Burns[16] emphasized that If there be actual dyspnea present you may be sure the disease is either not syncope anginosa (i e angina pectoris) or that it is a complicated case with effusion in the chest ossification of the valves or asthma ' Belching is common and the passage of flatus occurs occasionally at the end of the attack, these symptoms are usually accompanied by a sense of relief Occasionally there is a desire to urinate after the attack and there may be polyuria Dizziness faintness and rarely syncope may occur (syncope anginosa—Gallavardin)[35, 77] but they are not intrinsic elements of the attack Palpitation is very unusual unless the attack is precipitated by some form of paroxysmal tachycardia

Physical Signs

It is important to emphasize that there are often no abnormal physical roentgenologic or electrocardiographic signs in patients suffering from angina pectoris When the underlying disease is syphilitic aortitis or calcific aortic stenosis the physical signs are those of the underlying disease (q v) In patients with an underlying coronary disease hypertension is frequent and there may be corresponding physical roentgenologic and electrocardiographic evidences of left ventricular enlargement (Chapter 5) In patients with previous myocardial infarction there may be electrocardiographic changes and physical and roentgenologic signs of myocardial disease or of ventricular aneurysm

The *blood pressure* between attacks may be normal but is often elevated Hypertension was present in 44 per cent of Riseman and Brown's[101] cases of angina pectoris During the attack there may be a rise in blood pressure[65] but as a rule the blood pressure does not change The cardiac output circulation time and venous pressure are normal Usually also the *pulse rate* is unaltered during the attack but this is variable A rise in blood pressure and a rapid cardiac rate are essential features in the unusual attacks of angina pectoris occurring in certain patients with aortic insufficiency (p 686)

The Electrocardiogram in Angina Pectoris

The electrocardiogram of patients subject

to angina pectoris may differ during the attacks from that taken in the free intervals. Ordinarily electrocardiographic studies are made while the patient is free from pain; then they are entirely normal in the large majority of patients in whom there is no previous clinical history of myocardial infarction or heart failure.[107] However, there may be abnormalities of the T and Q waves or of the QRS complexes such as frequently accompany advanced coronary disease (p. 433) with healed myocardial infarcts and fibrosis, or evidence of left ventricular hypertrophy if there is an underlying hypertension or aortic valvular disease.

During a spontaneous or induced attack of angina pectoris the electrocardiogram usually undergoes significant and often characteristic alterations which disappear with subsidence of the attack.[31, 1.5, 98] The essential electrocardiographic abnormalities are (1) a depression of the RS-T interval and (2) diminished amplitude and eventual inversion of the T waves. The RS-T depressions and T wave inversions occur in the standard or precordial leads but are most common and most striking ... the left precordial leads.

In cases of acute myocardial infarction an ... segment depression in lead I or lead III is ...aracteristically associated with a discordant ...vation of the ST segment in lead III or lead ... respectively, and Q waves are present. ...owever, an occasional instance of discord...t ST elevation and depression resembling ...ose seen after myocardial infarction has ...en reported in cases of angina pectoris ... 504).[14, 97, 103] ST *elevations* are most likely ... occur during an attack of angina pectoris ...hen transient coronary insufficiency is ...vere or is superimposed on healed myocar...al infarction.

The RS-T depressions and T wave changes ... angina pectoris are determined by the oc...urrence of ischemia without necrosis and by ...e localization to most of the subendocardial ...egion of the left ventricle. The subendo...ardial region is involved because it has the ...oorest blood supply and is subjected to the ...ighest pressure during ventricular contrac...ion. Myocardial anoxia due to ischemia re...ults in disturbances in depolarization and ...epolarization which are represented by RS-T ...eviations and T wave changes. When the ...ubendocardial region is hypoxic, the resulting ...hanges are reflected in electromotive forces (vectors), which are recorded in the electrocardiogram as a depressed RS-T wave. When the subepicardial region is generally involved by hypoxia, as in pericarditis, an elevated RS-T segment is recorded. When the entire transmural myocardium of one wall of the left ventricle is involved, as in myocardial infarction, there are RS-T elevations in the leads facing the affected wall and depressed RS-T segments in those facing away from that wall. When a substantial portion of the myocardium undergoes death of tissue (necrosis), negative cavity potentials are recorded on surface electrodes and Q waves appear. Hence Q waves are absent as a rule in cases of angina pectoris.

Only occasionally is it possible to make electrocardiograms during a spontaneous attack of angina pectoris. However, electrocardiographic studies during paroxysms precipitated intentionally by exercise, rebreathing air or breathing air of low oxygen tension have revealed abnormalities similar to those observed in spontaneous attacks (p. 467). These abnormalities may appear even when these procedures do not produce the pain itself.

The Ballistocardiogram

Ballistocardiographic abnormalities of varying degree have been described as a regular finding in patients with angina pectoris (p. 62).[12, 107] The findings include exaggerated respiratory variations in the ballistocardiographic complexes, decrease in amplitude and loss of regularity or definitiveness. The ballistocardiographic complexes are especially likely to deteriorate in patients with angina pectoris after cigarette smoking.[65, 2] None of these changes is characteristic for angina pectoris and at the present time they cannot be regarded as being of diagnostic value.

ETIOLOGY AND PATHOLOGY

A variety of factors may be concerned in producing angina pectoris. They may be classified as (1) precipitating factors such as exercise, (2) underlying factors such as coronary artery disease, (3) contributory factors such as anemia, and (4) predisposing factors such as age, sex, hypertension, etc.

PRECIPITATING CAUSES OF ANGINA PECTORIS

1. Bodily Exertion

Physical exercise is by far the most frequent and most significant precipitating cause of

angina pectoris Often a patient reports that while running for a bus on his way to work or while walking up a slight incline to the subway station he suddenly and for the first time in his life experienced a severe oppressive pain behind the sternum which caused him to stop and which so terrified him that he returned to his home From then on the pain recurred whenever he ran or walked uphill or even on the level beyond a limited distance

Walking outdoors is the commonest form of bodily exertion producing the attack Sometimes the patient suffers pain if he walks up the slightest incline but not at all on the level, or he experiences an attack when he walks rapidly for a half block or more but he can walk a mile or more without discomfort if he proceeds very slowly To avoid embarrassment some patients walk along slowly and stop repeatedly pretending to be window-shopping Because of this the Germans have designated angina pectoris as the *schaufenster krankheit* For some patients the amount of exercise which can be performed without pain is remarkably constant Riseman and Stern [102] using a stair climbing test observed that when repeated examinations were made of a given patient with angina pectoris approximately the same amount of exercise was necessary to induce an attack On the other hand some patients find that when an attack has been provoked by exertion they can after a brief rest period, resume activity without further pain even when the exercise exceeds that which originally induced the attack

The severity or amount of exertion does not seem to be the sole factor determining the precipitation of an attack Some patients suffer pain on walking two blocks on their way to work and then are able to perform rather heavy manual work at their occupation indoors without discomfort It is notable that many sufferers of angina pectoris can avoid an attack on walking if they eat lightly or if they wait several hours after a meal but experience a paroxysm if they walk only a brief distance soon after a heavy meal The element of hurry may be an important factor Walking in cold weather or against the wind may provoke pain, whereas similar or greater activity causes no symptoms when the weather is warm Finding that their attacks are more frequent in the winter than the summer, many patients spend their winters in Florida or other warm climates thereby greatly reducing or avoiding attacks of angina pectoris In one patient with angina pectoris on effort severe attacks of typical angina pectoris were induced whenever he turned and lay on his right side but not when he was supine or turned on his left side

The occurrence of angina pectoris following bodily exertion depends on the increased cardiac output and the increased work of the heart resulting from exercise These are associated with a greater demand for oxygen by way of the coronary circulation Normally this increased demand is satisfied by a diminished coronary arteriolar resistance [4] with consequent increase in the coronary blood flow [4] However, in patients with angina pectoris some underlying disease such as coronary sclerosis which renders the vessels rigid and narrow prevents this normal adaptation so that the increase in coronary blood flow is not proportionate to the increased demand of the heart When the exercise stops the coronary flow is again adequate and the attack of angina pectoris subsides Following this transient myocardial ischemia caused by exertion there may be an increase in coronary blood flow (reactive hyperemia) which permits the patient to perform, without pain the activity which had just induced an attack of angina pectoris

According to Raab[99] effort (and likewise emotion and cold) induces angina pectoris by causing an influx of catechol amines into the myocardium (adrenosympathogenic effect) These are thought to cause an exaggerated expenditure of oxygen by their specific chemical effect, independent of the work of the heart

2 Digestion

It has been noted that after a meal especially if considerable food is ingested, less effort is required to provoke an attack than ordinarily and electrocardiographic and ballistocardiographic changes are induced in patients with angina pectoris [8] Since digestion like exercise increases the work of the heart, the relative deficiency of coronary blood flow caused by exercise is exaggerated when the exertion follows a meal Occasionally a heavy meal by itself induces an attack even though the patient is at rest In the normal person digestion is associated with an increase in coronary blood flow proportionate to the increased needs of the heart, but this compensation is apparently ineffective in patients

suffering from angina pectoris because of some underlying coronary or cardiac disease Kuo and Joyner[40] related angina pectoris after meals to postprandial lipemia which reached its peak at the time of the pain I am skeptical of this attempted causal correlation

3 Cold

Like digestion exposure to cold enhances the probability of an attack of angina pectoris after an amount of exercise which ordinarily is not followed by pain Exposure to cold produces this effect by increasing the cardiac output and work of the heart and thereby augmenting the need for oxygen [33] Gilbert and his associates[37] observed a diminution in coronary blood flow in decerebrate dogs following stimulation of the nasal mucous membranes with ice water This effect was prevented by previous vagal section or the administration of atropine They interpreted the reduction in coronary flow as resulting from a reflex in which the trigeminal fibers were stimulated on the afferent arc and the vagi on the efferent thus producing coronary vasoconstriction Freedberg and his co-workers[33] reduced exercise tolerance and precipitated angina pectoris by the local application of ice to the hand presumably causing coronary vasoconstriction Reflex stimulation of epinephrine with consequent increase in cardiac work could also account for the angina pectoris [17] Exposure of the skin surface to cold may rarely induce an attack of angina pectoris even without the additional factor of exercise This is observed in patients who experience pain on retiring if the room or bed clothes are very cold or on stepping into a cold bath

4 Emotion

While intense emotional states may provoke in neurotic persons various forms of pain in the cardiac area which are distinct from angina pectoris they may also and often do cause definite attacks of angina pectoris whether or not there is an associated neurosis Vigorous discussion heated arguments the excitement of card playing or of watching a football game or a horse race grief and anger and a variety of petty annoyances may all induce an attack Frequently cardiac pain occurs during sexual intercourse and rarely the attack is fatal

Like other factors precipitating angina pectoris excitement is believed to act by increasing the work of the heart in subjects in whom because of some underlying disease the coronary blood flow cannot be proportionately augmented The increased work of the heart may be due in part to the hyper secretion of epinephrine which is associated with emotional states

5 Tachycardia

When severe tachycardia occurs in paroxysms (paroxysmal atrial fibrillation paroxysmal nodal tachycardia) it may induce an attack of angina pectoris in persons with a diminished coronary reserve Rapid heart rates above 160 per minute augment the oxygen consumption of the heart because for any given minute output the oxygen need of the heart is greater at rapid than at slow rates Coronary flow may be impaired with reduction in the duration of diastole In patients whose coronary reserve is limited the added myocardial needs for oxygen resulting from the tachycardia cannot be satisfied through the normal accommodative mechanisms Then a definite attack of angina pectoris may be induced

6 Hyperinsulinism and Hypoglycemia

In diabetic patients with severe coronary atherosclerosis excessive insulin dosage may induce attacks of angina pectoris or even of myocardial infarction (p 497) Similar paroxysms of cardiac pain and associated electrocardiographic changes have been induced by spontaneous episodes of hypoglycemia due to hyperinsulinism (p 1034) The angina pectoris has been attributed both to disturbed cardiac metabolism due to the hypoglycemia and to an increase in the production of epinephrine in response to the low blood sugar [7]

7 Other Precipitating Causes

Attacks of angina pectoris have been ascribed to the administration of thyroid extract especially in patients with myxedema (p 1020) It has been indicated that epinephrine as well as insulin may cause cardiac pain Occasionally tobacco appears to precipitate paroxysms in susceptible individuals [1, 4, illegible, 15, 118] Smoking may produce this effect by increasing the heart rate and elevating the blood pressure [104, illegible, 115]

Many attacks of angina pectoris occur without apparent cause or in the course of ordinary conversation especially if it is prolonged Straining at stool is sometimes responsible Preliminary to an attack of acute myocardial infarction angina pectoris may increase in frequency and occur with little or no provocation (p 508)

Occasionally attacks of angina pectoris are precipitated by the recumbent position especially at night and the patient is forced to walk about or sleep in the sitting position in order to obtain relief The term angina decubitus has been applied to this type of cardiac pain, which may be precipitated by increased cardiac output and work associated with recumbency However there has been considerable confusion about this term which has also been applied to the precordial oppression associated with paroxysmal nocturnal dyspnea and to the pain accompanying acute myocardial infarction

UNDERLYING CAUSES OF ANGINA PECTORIS

The above-mentioned precipitating factors induce attacks of angina pectoris only as a rule in subjects who are susceptible because of some underlying cardiac disease Since angina pectoris is a symptom complex which may be due to a variety of diseases a complete diagnosis should include not merely the term angina pectoris but also the underlying causative disease The basic conditions which are usually responsible for angina pectoris are (1) coronary atherosclerosis (2) syphilitic aortitis with coronary ostial stenosis, and (3) aortic stenosis Angina pectoris has been associated also with anemias especially pernicious anemia with hyperthyroidism and hypothyroidism tachycardias hypertension and mitral stenosis But it is uncertain whether these conditions are basic causes or merely contributing factors in the production of angina pectoris Not infrequently two or more of the above diseases are combined and may be jointly responsible

1 Coronary Atherosclerosis (See Chapter 16)

Coronary atherosclerosis is by far the commonest pathologic basis of angina pectoris Either coronary thrombosis or severe narrowing produces pain by interfering with the blood supply of the myocardium The pathologic findings and their correlation with angina pectoris are discussed below (p 456)

2 Syphilitic Aortitis with Coronary Ostial Stenosis

This is discussed in Chapter 35 The occurrence of angina pectoris is determined by severe narrowing or obliteration of the aortic mouths of the coronary arteries The increased myocardial need for blood, due to the enlarged size and work of the heart caused by an associated aortic insufficiency is a predisposing factor

3 Aortic Stenosis

Aortic stenosis of the severe variety, so called calcific aortic stenosis is often manifested clinically by angina pectoris (see p 700) Contrary to general belief, angina pectoris is a relatively more common symptom of calcific aortic stenosis than of aortic insufficiency The incidence and pathogenesis of cardiac pain is discussed elsewhere (p 701)

4 Aortic Insufficiency

Syphilitic aortic insufficiency is much more apt to be associated with angina pectoris than is rheumatic aortic insufficiency It is probable that angina pectoris is rarely due to the aortic insufficiency per se, even though the low diastolic pressure associated with that lesion would be expected to impair the coronary blood flow Compensatory factors tend to restore an adequate blood supply (p 685)

In cases of syphilitic aortic insufficiency, angina pectoris is due chiefly to the usually associated coronary ostial stenosis (p 894) In some cases of rheumatic aortic insufficiency with angina pectoris an associated coronary arteriosclerosis may be responsible for the cardiac pain In both rheumatic and syphilitic aortic insufficiency the valvular lesion may be a contributory but not primary cause due to the increased work of the heart and the need for a larger blood supply In some instances an aortic stenosis is overlooked and aortic insufficiency is diagnosed because of the presence of an aortic diastolic murmur In cases of angina pectoris in young individuals with rheumatic aortic insufficiency vasomotor or autonomic crises associated with a sharp increase in cardiac rate and blood pressure may be responsible for the pain (p 686)

5 Other Causative Diseases

Anemia Among the uncommon causes of angina pectoris anemia appears to have the clearest relationship to the production of this symptom [48] Angina pectoris has been reported most often with pernicious anemia,[111] but it has been observed also with secondary anemias of varied etiology [6] I have seen angina pectoris due to severe anemia disappear after the anemia was cured following resection of gastric and sigmoid neoplasms [2] Nevertheless even with pernicious anemia angina pectoris is uncommon, and in most series of cases has not been noted at all Willius and Giffen[1 2] found a history of angina pectoris in 43 or 2 7 per cent of 1560 patients

with pernicious anemia. On the other hand Pickering and Wayne[35] reported that 7 of 25 ambulatory patients with severe anemia complained of pain in the chest induced only by exercise and relieved by rest. They suggested that angina pectoris might occur more frequently in patients with severe anemia if they were not stopped by breathlessness, giddiness or intermittent claudication before they exerted themselves sufficiently to produce anginal pain.

In almost all of the reports of angina pectoris associated with anemia in which the hearts were examined at autopsy, severe coronary atherosclerosis or syphilitic ostial stenosis was found.[47] The case reported by Elliot[5] appears to be an exception, but since the heart weighed more than 600 gm. and the anemia was moderate (57 per cent Sahli), the causal relationship of the anemia to the angina pectoris may be questioned. The infrequency of angina pectoris in cases of anemia, the usual finding of advanced coronary atherosclerosis at autopsy when angina pectoris had occurred during life, and the usually prompt termination of the attacks when the hemoglobin is elevated by transfusions or other therapy indicate that anemia can predispose or contribute to attacks of angina pectoris, but only when there is an underlying disease which impairs the blood supply of the heart.

In the presence of severe anemia, diminished coronary resistance and increased coronary flow compensate for the lowered oxygen content of the blood. In the presence of coronary stenosis this increased blood flow is limited and may become inadequate during increased work of the heart.[18]

Arterial Hypoxemia. Angina pectoris is rarely encountered in cyanotic patients with chronic pulmonary disease or congenital heart disease (hypercyanotic angina), the pain occurring with intensification of cyanosis during activity.

Hyperthyroidism and Hypothyroidism. Rarely angina pectoris has occurred in association with hyperthyroidism[62] or with myxedema.[63] In hyperthyroidism the pain is likely to occur during recumbency (angina decubitus) and is relieved by iodine, thiouracil or subtotal thyroidectomy.[110] The frequency of hyperthyroidism and the rarity of associated angina pectoris suggest that hyperthyroidism is at most only a contributory causative factor. It appears likely that the primary underlying cause of angina pectoris in these cases is coronary artery disease.

Coronary atherosclerosis probably accounts also for the occasional instances of angina pectoris and hypothyroidism, for the latter is often associated with coronary artery disease (p. 1017). But despite the frequency of coronary atherosclerosis, angina pectoris is uncommon in myxedema because the low metabolic rate results in a reduced myocardial requirement for blood. The relationship of myxedema to angina pectoris is discussed in the chapter on the former (p. 1020). Both the appearance and the relief of angina pectoris in myxedema have been attributed to thyroid extract (p. 1020).

Mitral Stenosis. Angina pectoris has been noted occasionally in cases of mitral stenosis.[6] Stuckey[114] reported 34 cases (8.5 per cent) of angina pectoris of effort among 400 patients with mitral stenosis and correlated the angina with a low cardiac output. Mechanical factors, such as compression of the left coronary artery between an enlarged left atrium and a dilated pulmonary artery, have been invoked to account for the angina pectoris. But considering the frequent occurrence of mitral stenosis and of angina pectoris as separate entities, the comparatively rare coexistence of the two conditions in the same patient must be explained as accidental, not causal, the former being usually due to rheumatic infection and the latter to independent coronary disease.

Angina pectoris has also been reported in cases of Friedreich's ataxia[29, 112] and other diseases occasionally associated with myocardial damage and cardiac hypertrophy.

CONTRIBUTING FACTORS

These are conditions which favor the occurrence of angina pectoris in subjects who are already susceptible because of coronary disease, syphilitic aortitis with coronary ostial stenosis or aortic valvular disease. The contributing factors, unlike the basic underlying causes, are by themselves incapable of producing angina pectoris and, unlike the precipitating factors, do not immediately initiate the individual attacks. These distinctions have not been and sometimes cannot be sharply drawn. Hyperthyroidism and anemia are two factors which, as I have indicated, may be properly considered as contributory factors in

the production of angina pectoris although they have also been reported as primary underlying causes

Diabetes predisposes to angina pectoris because of its relation to coronary atherosclerosis (p 425)

Hypertension is often found in patients with angina pectoris but usually the latter may be properly attributed to associated coronary disease *Hypertension is especially frequent in women with angina pectoris* (90 per cent or more in some series)[illegible], [21] Davis and Klainer[21] found an extreme degree of coronary disease involving two or more major arteries, in 95 per cent of non hypertensive patients with angina pectoris Similar severe coronary disease was observed in only 39 per cent of hypertensive patients with angina pectoris They concluded that if hypertension is present angina pectoris occurs frequently, even in the absence of severe coronary disease But in subjects with normal pressure angina pectoris is almost always dependent on the presence of severe coronary disease In other words severe coronary disease may by itself result in angina pectoris, if hypertension is associated angina pectoris may occur even when the coronary disease is of moderate degree The hypertension increases the work of the heart and leads to cardiac hypertrophy Both of these changes increase the requirements of the heart for oxygen In this way hypertension enhances the likelihood of angina pectoris if there is already some disturbance in cardiac circulation Similarly cardiac hypertrophy from any cause may increase the incidence of angina pectoris *Hypertension contributes indirectly to the occurrence of angina pectoris* by favoring the development of atherosclerosis of the coronary arteries[55] (p 428)

Familial Xanthomatosis and Hypercholesterolemia (p 1041) are frequently associated with angina pectoris because of the frequent and early occurrence of advanced atherosclerosis in these conditions (p 425)

Pheochromocytoma

Angina pectoris is occasionally observed in the rare cases of acute paroxysmal hypertension due to pheochromocytoma (paraganglioma) of the adrenal medulla (p 1025)

Disease of the Biliary and Gastrointestinal Tracts

The causal relationship of diseases of the gastrointestinal and especially of the biliary tract to angina pectoris has been stressed in recent years Chronic cholecystitis and cholelithiasis, duodenal ulcer, diaphragmatic hernia and organic and functional disturbances of the esophagus have been documented as causes of angina pectoris The symptoms of indigestion often associated with the attacks and their relief with eructation and the passage of flatus as the attack abates have suggested that reflexes from the esophagus stomach duodenum or colon could produce angina pectoris, perhaps by causing vagal vasoconstriction of the coronary arteries

This concept was supported by experimental observations that distention of the stomach with balloons decreased the coronary blood flow [3, 46] and that a similar procedure induced angina pectoris in humans These effects were prevented by previous section of the vagi or administration of atropine Electrocardiographic changes were observed in humans during experimental distention of the gallbladder[30] but not during manipulations of the biliary tract in operations on the gallbladder [31a] Recently experimental distention of the gallbladder in normal dogs caused no significant electrocardiographic changes but the same procedure produced marked RST segment deviation and increased height of T waves in dogs which had had a previous experimental coronary artery occlusion [60] Following a theory postulated by Verdon [117] the Jacksons[53] submitted experimental and clinical evidence that angina pectoris was caused by acute spasmodic uncoordinated contractions of the esophagus and stomach due to local gas traps and gaseous distention *The theory that disease of the biliary and gastrointestinal tract associated with the distention of these hollow viscera and vagal reflex coronary vasoconstriction can produce angina pectoris must be distinguished from the fact that normal digestion may precipitate angina pectoris in susceptible subjects* The latter can be explained adequately by the increased work of the heart during digestion independent of reflex action

The available data suggest that *disease of the biliary tract* is more common in patients who die of coronary disease (and angina pectoris) than in control groups of patients [11] Yet there is no proof that coronary disease causes gallbladder disease or vice versa or that a common etiologic factor is responsible for the association [118] Occasional cases have

been recorded in which anginal attacks and electrocardiographic abnormalities disappeared after cholecystectomy [28] It is probable that in these cases the diseased gall bladder acted only as a contributory cause of pain in the presence of underlying coronary or aortic disease In many cases of so-called angina pectoris due to gallbladder disease there is a failure to distinguish carefully between the pain radiation of cholelithiasis and cholecystitis and angina pectoris, as a rule the two can be clearly distinguished Occasionally common afferent pathways cause the referred pain of biliary disease to simulate that of angina pectoris or vice versa

Peptic ulcer is more often associated with coronary disease and angina pectoris than is generally recognized but the association may be no more frequent than a to be anticipated from the high incidence of the individual diseases Sometimes the anginal syndrome appears and recurs simultaneously with the activation of an old peptic ulcer and disappears when the ulcer is successfully treated [8] A bleeding ulcer[66] may precipitate angina pectoris in patients with coronary disease because of the induced anemia (p 1046)

Hiatus (paraesophageal) hernia has occasionally caused symptoms resembling angina pectoris [11] Careful analysis of the character location radiation and precipitating causes of the pain usually discloses distinctive differences from that of angina pectoris Resemblances may be due to the transmission of pain impulses from the esophagus over cord segments which are similar to those carrying pain impulses from the heart Occasionally hiatus hernia causes chronic esophageal or gastric bleeding and a severe secondary anemia in such cases the anemia may contribute definitely to the development of angina pectoris [9]

PREDISPOSING FACTORS

Age and Sex

At least 90 to 95 per cent of patients with angina pectoris are beyond the age of 40 and more than 70 per cent are beyond the age of 50 Angina pectoris in young persons (below the age of 30) has however been recorded [35] Eppinger and Levine [8] found the average age of onset of angina pectoris to be 56 for males and 58 for females and the range between 35 and 70 years

Angina pectoris occurs predominantly in males the ratio varying from 3 to 1 to 6 to 1 in different series [illegible] [31] As a rule angina pectoris occurs in females only when there is an associated diabetes or hypertension [115] but the number of exceptions appears to be increasing in my experience

Occupation Social and Economic Status and Race

These are discussed in connection with the basic diseases responsible for angina pectoris

Heredity (see under Coronary Atherosclerosis p 416)

Constitution and Temperament (see under Coronary Atherosclerosis p 416)

PATHOGENESIS

Although a variety of explanations have been offered for the mechanism of angina pectoris and although there is still some difference of opinion as to its exact pathogenesis the most widely accepted theory at the present time is that the pain and associated phenomena result from myocardial anoxia induced by coronary insufficiency [87]

Coronary Insufficiency and Myocardial Anoxia

Whenever the coronary blood flow quantitatively or qualitatively fails to keep pace with the myocardial needs coronary insufficiency is said to be present [15] Coronary insufficiency is thus defined as a disproportion between the blood supply and the blood requirements of the myocardium Coronary insufficiency is here employed as a physiological term and should not be confused with recent usage of this term to denote a purportedly distinctive clinical syndrome The latter is discussed below (p 461) Coronary insufficiency may be due to a diminution in coronary inflow an increase in the size and work of the heart a deficiency in the oxygen content of the blood or a combination of these The following are more specific causes of coronary insufficiency (1) coronary occlusion recent or old (2) coronary atherosclerosis with extreme narrowing (3) coronary ostial narrowing or occlusion due to syphilitic aortitis (4) aortic stenosis (5) conditions associated with a reduction in aortic blood pressure e g massive pulmonary embolism and other shock states (6) conditions associated with a reduction in oxygen content of the blood e g anemia arterial hypoxemia due to pulmonary or congenital

heart disease, carbon monoxide poison or low atmospheric oxygen tension (7) drugs e g epinephrine administered therapeutically or spontaneous epinephrinemia in cases of pheochromocytoma (p 1025)

Confusion has resulted from an attempt to limit the term coronary insufficiency to functional deficiencies in the coronary circulation thus excluding mechanical obstructions of the coronary artery i e coronary occlusion Angina pectoris which is one of the most striking symptoms of coronary insufficiency is due more often to old coronary occlusion than to any other cause Angina pectoris and coronary insufficiency are not synonymous Coronary insufficiency is a disturbance which under special circumstances may produce angina pectoris and under others myocardial necrosis or infarction or it may be documented only by electrocardiographic abnormalities unassociated with pain Coronary insufficiency necessarily denotes myocardial anoxia or hypoxia This should be emphasized because it is the myocardial anoxia which accounts for the cardiac pain of angina pectoris the necrosis of muscle and consequent fever leukocytosis etc in coronary thrombosis and the electrocardiographic changes associated with either coronary thrombosis or angina pectoris

Normally the coronary circulation is adequate for the myocardial needs at any given moment A wide range exists between the coronary flow under basal conditions and the larger flow when myocardial requirements are maximal This range may be termed the *coronary reserve* Under physiologic conditions the coronary flow can be augmented by certain compensatory adjustments which reduce the coronary resistance by dilating the coronary vessels Under pathologic conditions the development of a collateral circulation also helps to maintain an adequate myocardial blood supply but this may not be adequate under all circumstances When the coronary blood bed is attenuated by narrowing or obliteration of vessels or when the myocardial needs are increased by cardiac hypertrophy or valvular disease the range between basal coronary blood flow and maximal coronary blood flow becomes narrowed There may then be said to be a diminution in coronary reserve

When the coronary reserve is diminished to the point where the flow is adequate only for ordinary needs, any sudden further depletion of the blood supply or increase in myocardial demands may result in coronary insufficiency and myocardial hypoxia The coronary blood flow may be reduced by a fresh coronary occlusion by an acute hemorrhage or by a sharp reduction in blood pressure following massive pulmonary embolism acute pancreatitis, etc , or the myocardial blood demand may be augmented by bodily exertion excitement digestion cooling of the surface of the body or any other factor which exaggerates the work of the heart If the coronary insufficiency thus produced is sufficiently severe and prolonged the resultant myocardial anoxia may be followed by necrosis of an area of heart muscle (myocardial infarction) When however the coronary insufficiency is less severe and especially if it is transient e g with physical exertion or excitement, the resultant myocardial anoxia excites only certain temporary metabolic disturbances in the muscle which are completely or almost completely reversible Such episodes of acute transient coronary insufficiency are believed to account for the appearance of angina pectoris

According to this explanation the pain of angina pectoris and that of acute coronary occlusion (with myocardial infarction) are both due to acute coronary insufficiency the difference in duration and severity of the pain depending on differences in degree and duration of the coronary insufficiency That the pain of acute myocardial infarction and that of angina pectoris arise similarly from coronary insufficiency (with myocardial anoxia) is supported by (1) clinical resemblance (2) electrocardiographic evidences of myocardial impairment in spontaneous and induced attacks of angina pectoris (see below) and (3) the occasional discovery of foci of necrosis in the hearts of patients who died shortly after having suffered from attacks of angina pectoris[14]

Pathologic Basis of Coronary Insufficiency and Angina Pectoris

That the mechanism of angina pectoris was in some way related to coronary artery disease has been known since Jenner Black[4] Parry Burns[16] and subsequently others repeatedly found thickening calcification or obstruction in the coronary arteries of patients who had suffered from this symptom complex The relationship was obscured by the

frequency with which coronary atherosclerosis was found in individuals who had not suffered from angina pectoris during life and by the occasional occurrence of angina pectoris in individuals whose hearts disclosed normal coronary arteries at autopsy On the other hand Sternberg[114] invariably observed coronary artery disease at autopsy in cases of angina pectoris Braun[16] reported a series of 127 cases of angina pectoris in all of which there was severe coronary atherosclerosis Usually the narrowing was so pronounced that there was scarcely any lumen

Most of these discrepancies or uncertainties have been adequately clarified by the theory that angina pectoris is the result of myocardial anoxia due to a transient acute coronary insufficiency[17] That only a small percentage of cases of coronary sclerosis are associated with angina pectoris is due to the fact that significant interference with the blood supply to an area of myocardium (i e coronary insufficiency) can occur only when the vascular lumen is narrowed extremely or entirely obstructed Mann and associates[78] demonstrated that the internal diameter of a vessel could be decreased to one half its original diameter over a distance of 8 to 10 mm without reducing its blood flow significantly Even with complete obstruction of a vessel its area of supply may receive an adequate amount of blood through collateral anastomosing vessels provided that the obstruction became complete only after a long interval of slowly progressive arterial narrowing This is indicated by the studies of Blumgart Schlesinger and Davis[8] who demonstrated that angina pectoris occurred as a rule after two and exceptionally after one major coronary artery was occluded and the remaining major branches were severely narrowed Blumgart Schlesinger and Zoll[7] demonstrated that in cases of old coronary occlusion without a history of angina pectoris there was an average of 1 4 occlusions per heart whereas in cases of old coronary occlusion with a history of angina pectoris there was an average of 3 5 occlusions per heart These findings also support the probability that the onset of the first paroxysm of angina pectoris is due to an acute coronary occlusion without infarction or to an intimal hemorrhage with sudden marked increase in narrowing of the lumen rather than to gradual progressive narrowing Otherwise it is difficult to understand why a man who daily takes the same walk to his bus or train suddenly finds himself incapable of doing so without pain Frequently there is no pain until the occurrence of a clinical attack of acute coronary occlusion with infarction angina pectoris appears following convalescence and resumption of activity

The opposite circumstance that angina pectoris was sometimes observed in the absence of significant coronary artery lesions may be accounted for in several ways Recent improvements in the postmortem study of the coronary arteries have demonstrated that former investigators often overlooked severe coronary artery disease especially coronary artery occlusions Thus my own investigations with the late Dr Louis Gross and those of my associates[61] like those of Saphir et al[106] and more recently of Blumgart et al[6,7,124] have shown that multiple coronary occlusions are much more common than formerly believed and that the right coronary artery and left circumflex artery are occluded almost as often as the left anterior descending whereas older observers usually discovered occlusions only in the latter Sometimes also in coronary vessels which appeared patent throughout their course extreme narrowing or obliteration of the ostia due to syphilitic aortitis was formerly overlooked Furthermore it is now recognized that coronary insufficiency and angina pectoris may occur in the presence of normal coronary arteries as a result of other cardiovascular or valvular diseases which disturb circulatory dynamics so as to diminish the coronary blood flow or increase the myocardial requirement These other causative diseases such as aortic stenosis have been listed above

Evidence for the Theory of Myocardial Anoxia *(Secondary to Coronary Insufficiency)*

1 The pathologic data presented above are the strongest evidence for the belief that coronary insufficiency and resulting myocardial anoxia account for angina pectoris In most instances there is an actual mechanical interference with a major portion of the blood supply to the myocardium In the remaining cases there are pathologic abnormalities in the valves the heart or the circulation which lead to a diminution in coronary blood flow and an augmentation of myocardial blood

demand or an impoverishment of the oxygen content of the blood

2 That obstruction of the coronary circulation may cause pain was indicated by the experimental observations of Sutton and Lueth[116] on unanesthetized dogs These authors caused the animals to become restless and tachypneic and to behave as if they were in pain whenever they temporarily ligated a large coronary artery Furthermore temporary clamping of a coronary artery in experimental animals results in reversible electrocardiographic changes[30, 115] resembling those seen during attacks of angina pectoris in humans

3 Additional support is found in the similarity in character location and distribution of the pain in acute coronary occlusion and that of angina pectoris That the pain of the former is due to myocardial anoxia is readily accepted because of the pathologic finding of myocardial necrosis It is therefore probable that myocardial anoxia of less intense degree and briefer duration may be invoked to explain the similar but more transient pain of angina pectoris The observation of Buchner[14] that careful study will demonstrate focal necrosis of the myocardium in patients who had suffered from attacks of angina pectoris just before death indicates that the myocardial anoxia of angina pectoris may produce anatomic as well as functional alterations

4 More direct evidence that the pain of angina pectoris is due to myocardial anoxia was supplied by the experiments of Rothschild and Kissin[106] and of Dietrich and Schwiegk[33] These observers induced generalized anoxemia in patients who presented a history of angina pectoris or other evidence of coronary disease by having them rebreathe low oxygen mixtures or by placing them in a chamber with low oxygen tension In a high percentage of these cases an attack of angina pectoris was induced during the experiment and electrocardiographic alterations similar to those which occur when patients suffer spontaneous attacks of angina pectoris were observed With the administration of normal concentrations of oxygen, the pain disappeared and the electrocardiogram reverted to its previous appearance

5 Cases in which severe anemia either by itself or in association with underlying coronary disease provokes attacks of angina pectoris also support the theory that the latter is due to myocardial anoxia For the essential abnormality in anemia is reduction in the oxygen carrying power of the blood In at least some of these cases it has been shown that when the anemia is relieved by transfusion the attacks of pain cease promptly[5] It has also been shown that both in experimental and clinical carbon monoxide poisoning[1] in which the oxygen combination with hemoglobin is replaced by carbon monoxide electrocardiographic changes and myocardial necrosis occur similar to those observed in human cases of angina pectoris[illegible] Similarly in animals and humans exposed to high altitudes (above 5000 meters) corresponding to an oxygen saturation of the atmosphere of 80 per cent or less electrocardiographic changes occur which are similar to those seen with spontaneous or induced attacks of angina pectoris These observations indicate that it is the deficiency in oxygen which is the essential cause of angina pectoris

6 The pathogenesis of the pain in intermittent claudication of the lower extremities has been used by analogy to support the anoxic theory of angina pectoris In experiments simulating intermittent claudication MacWilliam and Webster[illegible] and Lewis Pickering and Rothschild,[66] showed that interruption of the arterial flow in the arm gave no pain if the arm was at rest However, if the arterial flow was reduced and the hand and forearm exercised pain occurred and was located not in the course of the artery but in the working muscle distal to the obstruction The observations were interpreted to indicate that the oxygen requirement of the *resting* muscle was satisfied even when the arterial flow was reduced, but that when the muscle was exercised the greater oxygen need of the active muscle could not be supplied with consequent appearance of pain By analogy, a patient with diminished coronary blood flow may have no pain at rest but suffers an attack of angina pectoris when the work of the heart is increased during bodily exertion

7 The theory of myocardial anoxia is compatible with the frequency of sudden death in patients with angina pectoris for it is generally believed that sudden death is usually due to ventricular fibrillation and the latter is especially favored by an oxygen deficiency of the myocardium[109]

Theory of Coronary Spasm It has been pro

posed that coronary arterial spasm is responsible for the actual attack of angina pectoris, whether or not there is underlying organic disease of the vessels[61, 84] The hypothesis of coronary spasm was invoked particularly to explain cases of angina pectoris and sudden death in which significant coronary lesions were not found at necropsy[6] It also appeared to account for attacks of angina pectoris occurring at rest especially those unassociated with tachycardia or an elevation in blood pressure or without any other apparent reason for diminished coronary blood flow or increased cardiac work Coronary spasm could also explain the sudden occurrence and disappearance of the paroxysm its reversible nature and its relief by vasodilator drugs such as the nitrites

Except for such rare unexplained occurrences as the complete disappearance of the radial pulse during an attack of angina pectoris[75] there is no significant positive evidence for the theory of coronary spasm since such spasm has never been observed Experimental evidence that distention of the esophagus or stomach may cause reflex vagal coronary vasoconstriction has been mentioned Prolonged vagal stimulation or administration of acetylcholine was reported to have produced severe coronary artery degeneration and thrombosis[24] These observations have been used to support a concept of coronary artery spasm due to vagal vasoconstriction Various specific objections to this hypothesis have been raised by Goldenberg and Rothberger[40] on the basis of their experimental studies

SITE OF ORIGIN AND CAUSE OF PAIN

It is probable that the pain of angina pectoris arises in the heart muscle although the aorta and the coronary arteries have also been implicated as the site of its origin

Sutton and Lueth[116] produced pain as manifested by restlessness and distress in unanesthetized dogs by temporary partial or complete constriction of a large coronary artery The pain was associated with rigidity and limping of the left foreleg signs which were interpreted as corresponding to the referred pain and muscle spasm in the left arm of humans with angina pectoris Whereas Sutton and Lueth concluded that the pain resulted from a diminished coronary flow to the myocardium other observers have suggested that the cause of pain following experimental coronary narrowing or occlusion was a direct stimulation of the nerve plexus surrounding the artery[88] or a distention of the coronary artery proximal to the obstruction associated with increased pressure in that segment[41] But Wiggers and Cotton[1] demonstrated that occlusion had no effect on the proximal coronary pressure and Sutton and Lueth[116] excluded coronary distention or pressure on the pericoronary nerves by producing pain in their dogs when the mouth of a coronary artery was plugged by a brass rod with a knob at its end These observations as well as the similar experimental observations of White Garry and Atkins[10] and of Shambaugh[109] and the data presented above to support the theory of myocardial anoxia lead to the conclusion that the pain associated with angina pectoris arises in the heart muscle and not in the aorta or coronary arteries

The exact *stimulus* which gives rise to pain is uncertain but it is most generally believed that it is a chemical one related directly or indirectly to the lack of oxygen in the muscle tissue However it is still undetermined whether the oxygen lack directly or whether the accumulation of metabolic products which are incompletely washed away by the coronary blood actually provides the stimulus for pain[74, 88, 46] In summarizing the various experimental and clinical observations on the pain of angina pectoris Katz[55] concluded that the stimulus responsible for pain is one or more acid metabolites such as lactic pyruvic or phosphoric acid or some non acid metabolite such as histamine phosphocreatine *adenosine or potassium which is formed* during cardiac contraction and accumulates in excessive amounts only when there is a relative oxygen deficiency

NERVOUS PATHWAY OF PAIN IN ANGINA PECTORIS

Recent anatomic and experimental studies and the effects of nerve block or excision in humans have added greatly to our still incomplete knowledge of the pathway by which pain is conducted from the heart A detailed discussion is presented in the monographs of White and Smithwick[11] and of Miller[82] The stimulus for the pain arises in the heart muscle itself but the pain fibers are located in a rich plexus in the adventitia of the coronary ar

teries and in the periarterial subepicardial tissue[49] Sutton and Lueth[118] and Katz, Mayne and Weinstein[58] demonstrated that after destruction of the pericoronary nerves by excision or painting with alcohol pain no longer appeared following experimental coronary occlusion in dogs

The pain impulses apparently are conducted only through the sympathetic nerves, although afferent as well as motor fibers are also present in the vagus. After reaching the periarterial nerves the pain impulses traverse the superficial and deep cardiac plexuses and then course through thoracic cardiac nerves to the upper four or five thoracic (paravertebral) sympathetic ganglia Other pain fibers from the cardiac plexuses extend in the superior middle and lower cervical cardiac nerves to the corresponding cervical sympathetic ganglia and then descend again to the upper four or five thoracic sympathetic ganglia

Having thus reached the upper thoracic sympathetic ganglia directly or indirectly the pain impulses enter the cord by way of the white rami communicantes which join these ganglia to the upper four or five thoracic spinal nerves As a practical basis for understanding the rationale of nerve block in the treatment of severe, protracted angina pectoris it should be recognized that all the nerve impulses arising in the heart and traversing the sympathetic nerves eventually converge in the upper four or five thoracic sympathetic ganglia and spinal thoracic nerves White Garry and Atkins[1] demonstrated that the pain caused by constriction of the anterior descending coronary artery in dogs could still be elicited after both vagi in the neck were cut or after the stellate ganglia and inferior portion of the sympathetic chains were resected However coronary constriction failed to result in pain following resection of the stellate and upper four pairs of thoracic sympathetic ganglia or resection of the upper five pairs of the thoracic posterior spinal roots These findings are in harmony with the observation that anesthesia of the above mentioned ganglia effectively relieves pain in humans with angina pectoris However the persistence of some of the pain in a minority of patients suggests that in these patients afferent nerve fibers carrying pain impulses from the heart may travel through the vagus and phrenic nerves[34]

THE PHYSIOLOGIC BASIS FOR THE PERCEPTION AND RADIATION OF ANGINAL PAIN

The pain arising in the heart eventually reaches the thalamic regions of the brain probably ascending in the spinothalamic tract of the cord It is believed that since the pain fibers from the heart join the spinal nerves before entering the cord the same segments of the cord (D1–D5) receive visceral pain sensations from the heart and somatic pain sensations from the corresponding areas of the body surface known as dermatomes According to the Mackenzie[73] theory of referred pain the pain impulses arising in internal organs are not perceived as originating in these organs but appear to arrive from the corresponding peripheral dermatomes which send afferent nerves to the same segments of the cord as the internal organ[73, 42] With respect to the heart, the corresponding surface area, chiefly D1–D4, includes the precordium the medial half of the anterior surface of the arm, the forearm and fifth finger However some of the pain arising in the heart may not be referred but may reach the thalamus directly and be perceived as arising in the heart This may account for the primary oppressive discomfort localized to the retrosternal region

The reason for the variations in the occurrence and radiation of the pain in patients with apparently similar coronary lesions is still unclear Undoubtedly these variations are due in part to individual differences in sensitivity to pain in general

The pain of angina pectoris which arises in the heart differs in quality from pains of somatic origin which are localized to similar areas of the chest wall and arms Pain is believed to be transmitted by slow conducting medullated (B group) and non medullated (C group) fibers[11] Differences in quality of pain may be determined by various possible combinations of B and C fibers which are simultaneously excited, the duller and more prolonged visceral pain representing a greater preponderance of excited non medullated C fibers The pain fibers running directly from the heart to the central nervous system may produce a special modality of pain, which differs from that perceived through somatic afferent radiations

Some of the distinctive features of the pain of angina pectoris and of associated phenomena are due to vagal and sympathetic efferent

and somatic motor reflexes which are initiated by the afferent pain impulses Reflex muscular spasm may account at least in part for the shoulder pain and weakness of the upper extremities as well as for the sense of compression and fixation of the chest wall The sense of strangling may in at least some cases be due to reflex spasm of the pharyngeal muscles Sweating and other vasomotor disturbances and gastrointestinal symptoms associated with angina pectoris may be due to vagal and sympathetic reflexes

ANGINA PECTORIS AND CONGESTIVE HEART FAILURE

There is no intimate relationship between angina pectoris and congestive heart failure In fact it is a common observation that patients with angina pectoris sometimes lose their pain when congestive heart failure develops Usually the manifestations of congestive heart failure especially dyspnea by considerably curtailing the patient s activities eliminate the chief precipitating factor of angina pectoris namely physical exertion On the other hand angina pectoris may persist or become intensified after the onset of heart failure This is likely to occur if the heart failure was induced by a coronary occlusion with myocardial infarction

So-called angina pectoris has been observed during attacks of paroxysmal nocturnal dyspnea (cardiac asthma) due to left ventricular failure[67] Some of these attacks of pain represent an acute coronary occlusion In other instances there is precordial discomfort due to acute dyspnea which however may not properly be termed angina pectoris Aside from these exceptions there are true instances of angina pectoris occurring at night in patients at rest and recumbent with or without concomitant paroxysmal dyspnea Acute left ventricular dilatation elevation of blood pressure tachycardia and consequent increased work of the heart have all been invoked to explain the occurrence of this angina pectoris so-called angina decubitus But the actual cause remains obscure

ANGINA PECTORIS AND INTERMITTENT CLAUDICATION

Since angina pectoris and intermittent claudication are both due to atherosclerosis and consequent arterial narrowing and occlusion both clinical syndromes may occur in the same individual However atherosclerosis in the coronary arteries and in the peripheral extremities are not usually equally extensive or equally complicated by narrowing or occlusion Furthermore limitation of activity by angina pectoris may prevent the clinical manifestation of intermittent claudication or vice versa McDonald[81] found that among 50 patients presenting with angina pectoris intermittent claudication was present in 4 and oscillographic evidence of occlusive arterial disease in an additional 8 Conversely among 79 patients presenting with intermittent claudication angina pectoris was manifested in 23 and electrocardiographic evidence suggesting ischemic heart disease but no angina pectoris in an additional 8

ACUTE CORONARY INSUFFICIENCY

The term acute coronary insufficiency is employed here to denote what is purported to be a distinct clinical pathologic entity[77, 78] It is presented not in concurrence with this concept but in acknowledgment of the widespread usage of this term Coronary insufficiency as a clinical entity is distinguished from coronary insufficiency a physiologic disturbance denoting an inadequacy of coronary blood flow for myocardial needs

The difficulty which many physicians experience in making an exact clinical pathologic diagnosis of a coronary episode based only on the clinical history examination and electrocardiogram accounts for much of the popularity of the diagnosis acute coronary insufficiency The ill defined diagnosis coronary insufficiency appears to solve this difficulty by providing a convenient term of diagnostic avoidance or evasion like the term rheumatism of old or the term collagen disease of more recent vintage the recourse of the physician who cannot make or will not attempt to make a more exact diagnosis of the underlying pathology There is danger that the diagnosis coronary insufficiency may lead to the false assumption that we have defined the nature of the disturbance by giving it a euphonious name when we really do not know exactly what has occurred

Definition of Terms

Unfortunately coronary insufficiency as a clinical pathologic concept has been variously defined[67, 78, 3, 77, 72, 79] In 1936 Levy and Bruenn[67] described under the heading acute fatal coronary insufficiency a series of

hospitalized patients with coronary heart disease who died suddenly but who at postmortem examination were found to have coronary atherosclerosis without fresh coronary occlusion In 1939 Büchner[15] described all forms of coronary attacks under the inclusive heading coronary insufficiency (*die Koronarinsuffizienz*[15]), but incorporated therein coronary occlusion and myocardial infarction as well as other severe and mild forms of coronary attacks without actual coronary occlusion In 1939 also Friedberg and Horn[34] described 37 cases of acute myocardial infarction without associated fresh occlusions of the coronary arteries chiefly in cases of pulmonary embolism and calcific aortic stenosis but also in severe acute anemia following operation and following a cerebral accident in patients with malignant hypertension Usually there were disseminated foci of necrosis or myomalacia involving chiefly the papillary muscles and subendocardial layers of the left ventricle The myocardial damage was attributed to intense coronary insufficiency due in part to the underlying coronary atherosclerotic narrowing and in part to the dynamics of the causative disease such as pulmonary embolism or aortic stenosis or the shock or anoxia of an operation severe acute anemia or a cerebral accident The term coronary insufficiency applied to the physiologic disturbance of an inadequate coronary blood supply but no clinical pathologic entity was implied

Chiefly on the basis of the electrocardiographic changes in the above cases of Friedberg and Horn[34] Master Gubner et al[78] attempted to differentiate acute coronary insufficiency (without coronary occlusion but with myocardial infarction) from coronary occlusion Subsequently Master and associates have been active in describing and popularizing acute coronary insufficiency as a complete entity with its own definite predisposing and precipitating factors its peculiar pathology and physiology characteristic electrocardiographic changes and requirements of distinctive treatment A careful review of their reports has not convinced me of the validity of this concept or of the justification of giving a new and clinical definition to a well established physiologic term Their cases form a motley group which are best classified clinically as angina pectoris (more or less severe or prolonged) or as myocardial infarction

Clinical Features

Acute coronary insufficiency is a diagnosis applied to a variegated group of attacks in which cardiac pain is more severe or more prolonged (more than 15 to 30 minutes) than in simple episodes of angina pectoris but without the typical signs or characteristic electrocardiographic pattern of myocardial infarction According to these criteria "acute coronary insufficiency is identical with 'coronary failure, an additional unnecessary term for cardiac pain intermediate between angina pectoris and myocardial infarct [13]

But Master and associates employ the term acute coronary insufficiency to include also patients who experience fever leukocytosis and accelerated erythrocyte sedimentation rate, and in whom myocardial necrosis is found at autopsy provided that the necrosis is not due to acute coronary occlusion Their assumption that there is no coronary occlusion is based on the electrocardiographic findings, which are not those of transmural (through and through) infarction

Acute coronary insufficiency is also applied to a group of cases in which cardiac pain may or may not be present but in which there are predisposing or precipitating factors, such as pulmonary embolism shock, hemorrhage or tachycardia and electrocardiographic changes indicating coronary insufficiency [79]

Electrocardiographic Changes

The diagnosis of "acute coronary insufficiency" is based frequently on the electrocardiographic finding of RS T depressions with or without T wave inversions in a patient with cardiac pain or with a disease known to impair the coronary blood supply The non specificity of such RS T and T wave changes is well known [64] Therefore coronary insufficiency is not a justifiable electrocardiographic diagnosis and is made by the electrocardiographer only with knowledge of the clinical history Even then the electrocardiographic changes should be interpreted in terms of myocardial, not coronary, disturbance The RS T depressions and T wave inversions in cases under discussion do not disclose the exact myocardial pathology, i e, whether necrosis is present or only ischemia but indicate only the localization of the myocardial disturbance, i e, in the sub-

endocardium The electrocardiographic changes may then be said to be due to subendocardial ischemia or necrosis Although subendocardial ischemia or necrosis often occurs without a recent coronary occlusion an acute coronary occlusion may produce subendocardial ischemia or necrosis rather than transmural infarction and may thus appear clinically and electrocardiographically as acute coronary insufficiency '

Even coronary occlusion with through and through (transmural) infarction may at the outset be characterized by electrocardiographic RS T depressions and T wave inversions In the presence of previous myocardial infarction or of left ventricular hypertrophy transmural infarction may be represented on the electrocardiogram by no more than ST depressions and/or T wave inversions Conversely and finally in coronary insufficiency without coronary occlusion there have been instances of through and through infarction with RS T elevations and Q waves in the electrocardiogram [19]

Conclusion

Acute coronary insufficiency is not a distinct clinical entity and adds confusion to cardiac terminology Terminology would be clarified if care were taken to distinguish a physiologic disturbance a pathologic lesion and a clinical picture Coronary insufficiency has long denoted a physiologic disturbance It may result from recent or old coronary occlusion extreme coronary narrowing non coronary cardiac diseases or from any factor which diminishes coronary blood flow reduces its oxygen content or increases myocardial work disproportionate to coronary blood flow This is too broad a category to define a specific myocardial lesion or a specific clinical entity

Coronary thrombosis or occlusion refers to a pathologic lesion It is sometimes employed to denote a clinical picture namely the symptoms and signs of the resulting myocardial infarction It would be preferable not to use the term coronary occlusion in a clinical sense because it may or may not be followed by myocardial infarction and the clinical picture varies significantly according to the variable myocardial disturbances Myocardial infarction is a term used to describe a pathologic change but also a clinical (including electrocardiographic) picture because the clinical and electrocardiograph features are actually determined by the infarct varying only with the extent and location of the myocardial injury

Angina pectoris is a clinical syndrome Its underlying pathology is variable but most commonly comprises coronary occlusion severe coronary narrowing calcific aortic stenosis or syphilitic ostial stenosis It may be induced by any disease or disturbance causing coronary insufficiency Coronary insufficiency is the physiologic disturbance underlying angina pectoris as it is the physiologic disturbance underlying myocardial necrosis or infarction The coronary insufficiency underlying angina pectoris is transient relatively less intense and essentially irreversible as compared with the usually permanent and severe myocardial destruction accompanying myocardial infarction

The diagnosis *angina pectoris* (or persistent angina pectoris) should be employed even when a patient experiences cardiac pain which is more prolonged than the ordinary attack of angina pectoris provided fever leukocytosis and shock do not develop and the characteristic signs of myocardial infarction are absent But one should make a careful search for the possible factor which accounts for the longer duration of the pain Often this may be a coronary occlusion which has induced myocardial ischemia but not infarction because collateral circulation maintains the viability of the affected muscle

When RS T depressions with or without T wave inversions occur in a patient with cardiac pain or a condition known to produce coronary insufficiency a diagnosis of (subendocardial) myocardial ischemia or necrosis should be made If fever leukocytosis shock etc develop the diagnosis is subendocardial infarction not merely ischemia In the presence of marked left ventricular hypertrophy or previous myocardial infarction ST depressions and T wave inversions may occur even with transmural infarction

There is no need for the term acute coronary insufficiency to denote a clinical entity and such usage should be abandoned Coronary insufficiency should be employed only to designate the physiologic disturbance caused by an inadequate or unoxygenated coronary blood flow In clinical diagnosis designation of the physiologic disturbance is

inadequate, it is essential to indicate as clearly as possible the underlying myocardial pathology and the etiologic factors

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Chapter 18

ANGINA PECTORIS

Diagnosis, Differential Diagnosis, Prognosis and Treatment

DIAGNOSIS

The identification of a pain or distress in the chest as angina pectoris does not constitute a complete diagnosis for angina pectoris is a symptom complex and not a disease However the recognition of angina pectoris is an important diagnostic step since its presence denotes some serious underlying cardiac ailment usually severe coronary atherosclerosis with or without occlusion

THE CLINICAL HISTORY

The diagnosis of angina pectoris depends primarily on the clinical history and not on objective findings However the presence of an underlying cardiac disease or a positive response to tests disclosing coronary insufficiency supports the diagnosis of angina pectoris

The essential diagnostic features of angina pectoris are (1) the paroxysmal occurrence of the pain (2) its brief duration (3) its characteristic location radiation and quality (4) its precipitation by effort and relief by rest and (5) its relief by nitrites

These points require brief annotation (1) Sometimes there is a dull persistent pain or ache between the paroxysms varying in intensity but there must also be definite paroxysms to warrant the diagnosis of angina pectoris

(2) Attacks of angina pectoris usually last less than five minutes and rarely exceed fifteen minutes Apparent paroxysms of angina pectoris of longer duration probably denote an acute coronary occlusion without infarction or impending myocardial infarction even when there are no significant electrocardiographic abnormalities At other times prolonged attacks of angina pectoris denote that the predisposing or precipitating factor is persisting longer than usual Finally, as a rule severe or prolonged cardiac pain indicates an acute coronary occlusion with myocardial infarction, which will be disclosed by characteristic clinical and electrocardiographic findings (Chapter 20)

(3) The location of the pain over the sternum or precordium is characteristic but not specific for angina pectoris Radiation to the left shoulder arm and wrist or both arms is usually confirmatory of angina pectoris but not essential for the diagnosis The strangling constricting or compressing quality of the pain and the frequent association of angor animi are valuable diagnostic features Dull or sticking pains and pain in the region of the cardiac apex in the lower part of the left axilla or below the left breast are rarely manifestations of angina pectoris

(4) The diagnosis of angina pectoris is equivocal if there is no history of the precipitation of the pain by effort and its relief by rest But sometimes no such history is elicited because the patient has avoided all but the mildest activity or because he has not walked far enough or rapidly enough to induce pain He should be asked specifically Do you have pain on walking rapidly on hurrying or on walking uphill? Can you continue the same pace once the pain begins? Is it relieved by slowing your pace or by stopping? When the pain is induced by walking it has an arresting quality which compels the patient to stop or sharply reduce his speed The pain of angina pectoris occurs frequently with vigorous or prolonged conversation especially on the telephone and with excitement anger or other emotional states This relationship should not be interpreted as indicating that the pain is psychogenic especially if there are other occasions when the pain is produced in typical fashion by effort and relieved promptly

by rest. Pain induced *only* by emotional states is often due to angina pectoris if its quality, location and radiation are characteristic, but it should be brief and paroxysmal and relieved promptly by nitroglycerin. It may be necessary to test the effect of effort and rest in order to be certain of their relationship to the pain. Sternal or precordial pain which is induced by fatigue or after working long but which is not promptly relieved by rest should not be interpreted as a manifestation of angina pectoris. Similarly, anterior chest pain which occurs only or especially when the *patient sits down and relaxes after a hard day* is not angina pectoris. Reproduction of the pain by rapid walking under appropriate circumstances and its prompt relief by rest help to confirm the diagnosis of angina pectoris. On the other hand, reproduction of the pain by direct pressure over the costochondral *junctions, by special motions of the chest wall, neck or left arm, or by hyperventilation* serves both to exclude the diagnosis of angina pectoris and to reassure the patient.[85]

(5) The response to nitrites, especially nitroglycerin or amyl nitrite, is often helpful in diagnosis. The diagnosis of angina pectoris is *supported if the relief of the pain, pressure* or indigestion, is definite, prompt and unquestioned by the patient. I have, however, observed patients suffering from pain in the chest which was relieved by nitroglycerin but which was later proved to be unrelated to cardiac or coronary disease. However, this is extremely *uncommon and care should be* taken to evaluate the effectiveness of the nitroglycerin by repeated trials and by timing its onset of action and relief. If the pain occurs regularly under given circumstances, prevention of the pain by prophylactic administration of nitroglycerin just be*fore the pain is apt to occur is confirmatory* of angina pectoris.

OBJECTIVE EVIDENCES OF CARDIAC DISEASE

When the essential symptomatic criteria are satisfied, the diagnosis of angina pectoris *may be made with certainty even in the* absence of objective findings. In doubtful cases of pain in the chest, however, a suspected diagnosis of angina pectoris may be supported by finding hypertension, significant cardiac enlargement, aortic valvular disease or such electrocardiographic abnormalities as frequently accompany severe coronary artery disease (see p. 433). Occasionally it is possible to take an electrocardiogram during an attack of pain; the presence of a transient ST de*pression and lowering or inversion of the T waves with a return to normal soon after the* pain subsides strongly suggest that the pain is a manifestation of angina pectoris. Occasionally RS-T elevations have been observed during an attack of angina pectoris resembling those commonly seen with acute myocardial infarction[1,8,82,89] (p. 522). However, it should be stressed that angina *pectoris due to advanced coronary* atherosclerosis may be present without abnormal physical signs in the heart and without roentgen ray or electrocardiographic evidence of myocardial disease in more than one quart[er] of patients. When patients are observed early in the course of their angina pectoris *and there is no history of previous myocardial infarction*, there may be no objective abnormalities in at least 75 per cent of cas[es].

TESTS OF CORONARY RESERVE AND CORONARY INSUFFICIENCY

It has been mentioned that ther[e] ... margin of safety whereby a diminutio[n] ... *coronary blood flow or an increa[se]* ... myocardial blood requiremen[ts] ... without resulting in coronary ... angina pectoris. This margin ... coronary reserve. In subjects ... impaired coronary circulatio[n] ... reserve is already so dimin[ished] ... *factor tending to cause anox[ia]* ... result in myocardial anoxia ... duce angina pectoris or che[st] ... changes. This principle has ... the basis of tests for corona[ry] ... The demonstration of a di[minished] ... reserve by such tests, ... *pain suggesting angina* ... as supporting the con... actually represents an ... the factors utilized t... sufficiency in patient[s] ... onary reserve are ge[n] ... exercise. These tests ... *very small percenta[ge]* ... pectoris an accura[te] ... always possible on ... history and routi[ne] ... mented if necess[ary] ... between which th[e] ...

the circumstance under which the pain occurs, its character location, radiation and duration and the effect of rest and nitroglycerin The statement that the history is *often* atypical and not diagnostic is certainly not valid in my clinical experience However, objective tests are useful in problems of insurance and medicolegal practice because of the possibility that a history of angina pectoris may be fabricated

Anoxemia Test (Hypoxemia Test)[67, 46, 110, 108]

Generalized anoxemia is induced by having the subject breathe a mixture of 10 per cent oxygen and 90 per cent nitrogen for 20 minutes unless cardiac pain is experienced before electrocardiographic abnormalities are noted, according to the criteria of Levy[61] (1) The sum of the RS 1 deviations in leads I II, III and V_4 exceeds by 3 mm or more that of the control According to several observers, there is usually not more than 0 5 mm and never more than 1 mm displacement of the RS T segment in any standard lead in normal individuals (2) There is partial or complete reversal of the direction of the T wave in lead I accompanied by an RS T deviation of 1 mm or more in this lead (3) There is a complete reversal of the T wave in lead V_4 regardless of any associated RS-T deviation in this lead Burchell and his as

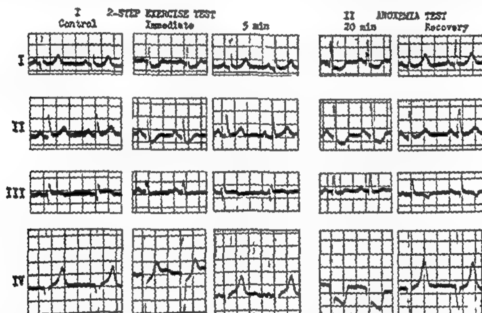


Fig 98 Exercise and anoxemia test in coronary artery disease on same patient Positive test for coronary insufficiency with both tests Pronounced S T segment depressions

that interval ■ Turner and Morton[110] suggest *that 10 minutes suffice The subject is per*mitted to breathe 100 per cent oxygen for one minute immediately after concluding the test or if there are any unpleasant reactions Electrocardiograms are taken just before the test and at five-minute intervals until the electrocardiogram has returned to its control form It has been recommended that the "arterial" oxygen saturation during the test be controlled with the aid of an ear oximeter and that the oxygen saturation should be maintained at 75 per cent[110] or 70 per cent[107, 76] The test ■ termed positive (Fig 98) and considered indicative of coronary insufficiency or diminished coronary reserve if pain occurs during the procedure or if the following sociates[17] found that the precordial leads were more informative than the standard leads and could be used exclusively if desired According to Turner and Morton[110] an S T depression of 2 mm or more in lead V_4 indicates a positive test, but other leads should also be recorded Characteristic chest pain during the test is probably due to coronary insufficiency and as a rule is accompanied by the diagnostic electrocardiographic changes, but frequently these electrocardiographic abnormalities appear without pain The S T depressions appear to denote that myocardial anoxia is most pronounced in the subendocardial layer and that this is electrically positive relative to the subepicardial layer A negative test does not exclude angina pectoris

or coronary insufficiency. As a matter of precaution, it is both unwise and unnecessary to perform an anoxemia test in a patient whose 12 lead electrocardiogram discloses abnormalities indicative of myocardial damage.

Patterson, Clark and Levy[75] found the test to be electrocardiographically positive in 49 per cent of 157 cases of coronary sclerosis. In an additional 20 per cent the occurrence of pain without electrocardiographic changes also offered presumptive evidence of coronary insufficiency. Compared to this total of 69 per cent positives in patients with coronary disease, there was no instance of pain or a positive electrocardiographic test in 136 normal subjects. Other observers have obtained positive tests in 30 to 50 per cent of cases with probable or definite clinical coronary disease, in 15 to 20 per cent of suspected cases and in 0 to 2.7 per cent of normals or slightly suspected cases.[9] Bjorck[10] observed a positive anoxemia test in 9 patients with cardiac neurosis without organic heart disease. There was a negative response when 0.5 mg. ergotamine tartrate was given intramuscularly or subcutaneously 20 minutes before the anoxemia. Dihydroergocornine (0.5 mg.) has been similarly used.[75]

Although occasional unpleasant and even serious reactions have been observed during the hypoxemia test[116] (dizziness, headache, drowsiness, nausea, cyanosis, anxiety, numbness, tingling, restlessness, hysteria, vasovagal syncope, air hunger, chest pain, arrhythmia, convulsions and pulmonary edema), the serious ones have become rare as technique has improved and been standardized and discretion used in the choice of subjects. *Burchell and his associates*[17] *performed* 730 hypoxemia tests without a fatality. Among the contraindications to the anoxemia test are obvious cardiac enlargement, definite previous myocardial infarction, chronic pulmonary disease, severe anemia, cyanosis, pregnancy, acute illness, advanced debility. Because of the risk of reactions, however small, the need for technical equipment and special skill in the choice of patient and in the interpretation of findings, the anoxemia test is not yet suitable for general use.

Exercise Test of Coronary Reserve[86, 111, 85]

Exercise strains the coronary reserve by increasing the myocardial need for blood. A standardized amount of exercise is performed (e.g., the two-step test of Master and Oppenheimer[67] or that of other authors[87, 103a]). In patients with a diminished coronary reserve the exercise may produce pain or distinctive electrocardiographic changes.[111, 86] The test is not performed until a resting electrocardiogram has been taken and found to be normal. A positive test is associated with the following changes according to Sokolow and Twiss[111]:

(a) RS-T segment depression or elevation of 1 mm. or more in lead I, of 1.5 mm. or more in lead II, of 1.5 mm. or more in lead III and 2 mm. or more in lead IV. The base line at the beginning of the QRS, i.e., the P-Q segment, is used as the reference level determining S-T deviations. (Note also that Scherf and Schaffer[9] regard an S-T depression of less than 2 mm. as *not* definitely abnormal.)

(b) The conversion of an upright to a diphasic or inverted T wave in lead I, II or IV.

(c) The development of bundle branch block. Right bundle branch block has been observed during spontaneous attacks of angina pectoris and after exercise in patients with clinical coronary disease.[9]

Twiss and Sokolow[111] reported that cardiac pain developed during the test in 45 of 66 patients known to have angina pectoris. The above mentioned significant electrocardiographic abnormalities appeared in two thirds of those who experienced pain during the test and in 56 per cent of the total number of patients with angina pectoris regardless of the development or absence of pain.

The two-step exercise electrocardiogram test *as described by Master*[86] *involve the* performance within 1½ minutes of usually 15 to 25 trips up and down two steps each 9 inches high. He stresses the importance of standardizing the amount of exercise, the number of trips being varied with the age, weight and sex of the patient according to published tables. The exercise is stopped promptly if the patient experiences pain. The test is performed only if the resting 12 lead electrocardiogram is normal and there is no history suggesting recent or impending myocardial infarction. If the so called single two step electrocardiogram as just described is negative, a double two-step test is administered; this involves twice as many trips as in the single test but in three minutes instead

the circumstance under which the pain occurs, its character, location, radiation and duration and the effect of rest and nitroglycerin. The statement that the history is *often* atypical and not diagnostic is certainly not valid in my clinical experience. However objective tests are useful in problems of insurance and medicolegal practice because of the possibility that a history of angina pectoris may be fabricated.

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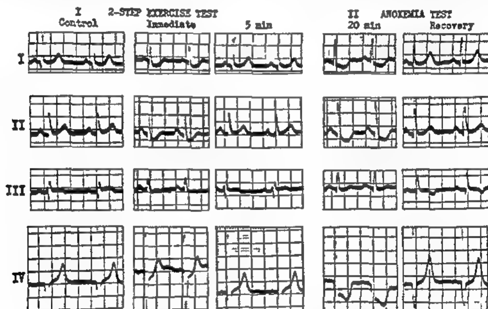
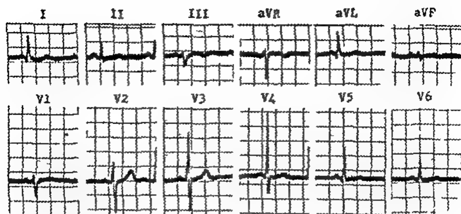
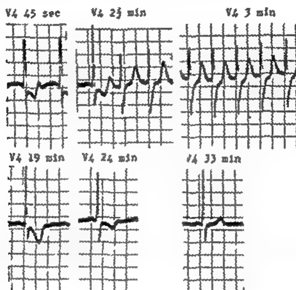


Fig 98 Exercise and anoxemia test in coronary artery disease on same patient. Positive test for coronary insufficiency with both tests. Pronounced S-T segment depressions.

that interval.[81] Turner and Morton[110] suggest that 10 minutes suffice. The subject is permitted to breathe 100 per cent oxygen for one *minute immediately after concluding the test* or if there are any unpleasant reactions. Electrocardiograms are taken just before the test and at five-minute intervals until the electrocardiogram has returned to its control form. It has been recommended that the "arterial" oxygen saturation during the test be controlled with the aid of an ear oximeter and that the oxygen saturation should be maintained at 75 per cent[110] or 70 per cent.[107, 76] The test is termed positive (Fig 98) and considered indicative of coronary insufficiency or diminished coronary reserve if pain occurs during the procedure or if the following sociates[17] found that the precordial leads were more informative than the standard leads and could be used exclusively if desired. *According to Turner and Morton*[110] an S-T depression of 2 mm or more in lead V_4 indicates a positive test but other leads should also be recorded. Characteristic chest pain during the test is probably due to coronary insufficiency and, as a rule, is accompanied by the diagnostic electrocardiographic changes but frequently these electrocardiographic abnormalities appear without pain. The S-T depressions appear to denote that myocardial anoxia is most pronounced in the subendocardial layer and that this is electrically positive relative to the subepicardial layer. A negative test does not exclude angina pectoris





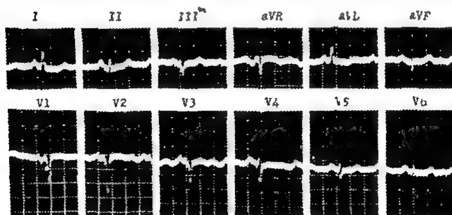


Fig. 99 Acute myocardial infarction following two-step exercise electrocardiogram

1-23-56 *Normal electrocardiogram in a 62 year old man with 5 year history of chest pain interpreted as angina pectoris*

1-26-56 Following repeat normal electrocardiogram Master single two-step exercise test Marked ST depressions paroxysmal tachycardia and chest pain Relief and normal electrocardiogram only after nitroglycerin 30 minutes after completion of test

1-27-56 Chest pain recurred shortly after completion of test and persisted until the next day Electrocardiogram shows first of records of progressive changes of anterior wall myocardial infarction

injury to the pectoralis minor tendon (5) Peptic gastric or duodenal ulcer (6) Cholelithiasis and chronic cholecystitis (7) Esophagospasm (8) Diaphragmatic or paraesophageal hernia (9) *Bronchial asthma* (10) Radiculitis secondary to cervical dorsal spondylitis or displaced cervical disk (11) Subacromial bursitis or periarthritis of the left shoulder (12) Cervical rib (13) Scalenus anterior syndrome (14) Metastatic cervical lymph nodes compressing the brachial plexus (15) Pleurisy (16) Pericarditis (17) Aneurysm of the aorta (18) Carcinoma or suppuration of the lung or *mediastinal neoplasm* (19) Diaphragmatic flutter[13] (20) Carotid sinus syndrome[23]

The differentiation of angina pectoris from acute myocardial infarction will receive special discussion (see p 554)

Relation of the Pain to Exertion

Pain in the above conditions is chiefly distinguished from angina pectoris by being unrelated to general bodily exertion especially walking rapidly or uphill The pain secondary *to subacromial bursitis arthritis of the* shoulder and spine or local disease of the chest wall may be precipitated by exercise of the local areas but not by general bodily effort Active or passive movement of the left arm or cervical and thoracic spine through its complete range of motion or deep inspiration coughing or sneezing may reproduce the pain and disclose its noncardiac origin, immobilization of the affected part may eliminate or diminish the pain even during general bodily exertion Reeves *and* Harrison[63] have stressed the diagnostic and therapeutic value of the *reproduction of the patient s chest pain* The occurrence of the pain with emotional states is not decisive being as common with neuroses and functional disturbances of the gastrointestinal tract as with angina pectoris, but the character location and radiation of the pain are often different

Character and Location of the Pain

The character and location of nonanginal chest pain often aid in differentiation from angina pectoris A dull ache in the precordial *region or* above and to the left of the heart is common in neurotic persons or as a result of *pectoral myalgia or neuralgia A dull ache* or sharp, sticking or stabbing pain in the region of the cardiac apex or *in the left breast* also occurs frequently in neurotic subjects In addition, there is often a complaint of excessive fatigability, palpitation, diffuse pains in different parts of the body and difficulty in taking a deep breath (characterized objectively by sighing respiration) The pain often *radiates around the ribs and to the left subscapular region* In addition to the difference in site and character of this pain it is usually indefinite in onset as compared with the paroxysmal nature of the attacks in angina pectoris The pain occurs at rest as well as with effort and especially when the patient is fatigued There is often an hyperesthesia in the painful area, usually in the segmental *distribution of D4 and D5 rather than of* C8 and D1 as in angina pectoris A similar type *of pain occurs in subjects with indigestion* especially in middle-aged obese men and women This form of pain, often in association with other diffuse pains variously located in the chest and abdomen, results from gastrointestinal gaseous distention

Dull and sticking precordial pain or discomfort usually associated with palpitation frequently results from paroxysmal *tachycardias* and *runs of premature beats* However with very rapid ventricular rates, ectopic tachycardias may induce myocardial ischemia and true anginal pain A careful history and examination readily disclose the relation of the pain to the arrhythmia

The pain of gastric and duodenal ulcer is usually situated in the epigastrium and lower sternal region, it has a burning or boring quality is unrelated to effort and occurs usually one to four hours postprandially whereas *angina pectoris is apt to* occur more promptly after meals and usually *only with postprandial exertion Ulcer* pain ordinarily is relieved rapidly by alkalis and milk

The patient with bronchial asthma may describe substernal pain or pressure on rapid walking which may be interpreted as angina pectoris A careful history and examination and the effectiveness of sublingual Isuprel and the ineffectiveness of sublingual nitroglycerin usually differentiate the two conditions

The pain due to pleurisy or pericarditis is unlikely to be confused with angina pectoris because of associated clinical symptoms, the *presence of fever and other objective evidences* of infection and local disease the sharp nature *of the pain and its frequent occurrence* with deep inspiration

Expanding or dissecting aneurysms pro-

duce a more constant crushing type of pain than is associated with angina pectoris

Occasionally I have seen cases of carcinoma or suppuration of the left upper lobe of the lung with chest pain interpreted as angina pectoris The pain is usually more intense and persistent than that of angina pectoris although it may be located in the precordium and may radiate to the left upper extremity

Differentiation of Local Lesions of the Chest Wall by Physical Examination

Physical examination often reveals the local origin of pectoral pain Careful palpation of the ribs may disclose a fracture due perhaps to a metastatic lesion or involvement by a myeloma Examination of the costochondral junctions especially on the left side may demonstrate that the pain is due to an arthritis or to a traumatic non-suppurative painful swelling of one or more of these joints (Tietze's syndrome[6, 7, 10]) or to a fibrositis This occurs more commonly than is generally recognized Local infiltration of 1 per cent procaine often relieves the pain but similar relief has been reported in cases of angina pectoris Occasionally digital manipulation may demonstrate that the slipping of one rib under another is the cause of precordial pain The pain is usually prevented by strapping the affected chest wall A slipping rib cartilage[67] may also cause chest pain which has been confused with angina pectoris Usually the cartilages of the eighth ninth or tenth rib are involved having been dislocated or displaced by fracture The pain can be reproduced by digital examination with the patient supine his knees flexed Manipulation of the movable rib cartilage causes pain and an audible click The pain may be cured by strapping or resection of the affected cartilage Strain of the left pectoralis minor muscle was described as a common cause of chest pain in soldiers[69] Skeletal pain may be distinguished by the relief obtained following procaine infiltration of local tender areas or between the spinous processes of the lower cervical and upper thoracic vertebrae[84]

Roentgenologic Differentiation of Biliary Gastrointestinal Aortic Pulmonary and Skeletal Disease

The underlying cause of many types of chest pain is often determined or proved by roentgenologic examination This applies to cholelithiasis peptic ulcer diaphragmatic or esophageal hernia aortic aneurysm pleuropulmonary disease subacromial bursitis arthritis of the left shoulder or cervicodorsal spine or destructive lesions of the ribs Roentgenologic examination of the chest including its bony cage of the cervical spine and left shoulder joint and of the esophagus stomach duodenum and biliary tract are often essential to the accurate interpretation of pain simulating angina pectoris but the similarity in pain is usually very superficial It is also important to remember that the patient with duodenal ulcer hiatus hernia and other conditions may also be suffering from angina pectoris A careful history and therapeutic tests differentiate the two types of pain

Differentiation of Angina Pectoris from Pain Due to Skeletal Lesions

Various forms of cervicodorsal neuritis may produce pain which is mistaken for angina pectoris This pain is rarely retrosternal is usually sharp or aching in quality and has no paroxysmal relation to general bodily exertion One fairly common and often unrecognized cause of pain referred to the precordium and left arm is a traumatic or postural strain of the muscles and ligaments about the lower cervical and upper dorsal spine An underlying spondylitis displaced cervical disk or other lesions of the vertebrae or articulating surfaces may also be present[71] There is often a history of stiff neck The disturbance may also cause occipital headache or pain of the upper back But the chief pain is usually in the left shoulder arm forearm fingers and upper precordium[84] Relief of the pain may be obtained by the application of a cervical collar supporting the skull or by suspension in traction Semmes and Murphy[92] described a syndrome simulating angina pectoris and characterized by pain in the neck left shoulder and arm and precordium and by sensory changes in the index and middle fingers due to unilateral rupture of the sixth cervical intervertebral disk The pain was due to compression of the seventh cervical nerve root on the left side Cure or relief was effected by subtotal hemilaminectomy under local anesthesia

Sometimes advanced osteoarthritis or destructive lesions of the upper dorsal spine or lesions of the spinal cord or nerve roots produce radicular pains of the precordium[4, 2] These pains occur in band like zones which are usually complete and involve the anterior

and posterior chest wall corresponding to the involved nerve segments Often there is a similar band like area of objective hyperalgesia (Head zone) which has a complete or incomplete segmental distribution Angina pectoris is more likely to produce pain radiations which skip from one root zone to another and its segmental distribution is usually incomplete The pain due to spinal lesions is not related to general bodily effort but is induced by motions of the spinal column or by factors increasing intraspinal pressure such as coughing and sneezing

Periarthritis of the shoulder joint subacromial bursitis and calcification of the shoulder tendons are common lesions often associated with pain not only about the shoulder but also in the arm and anterior chest wall When the left shoulder is involved the pain may be interpreted as angina pectoris Ordinarily the precipitation or exaggeration of the pain by elevation or rotation of the arm the limitation of motion about the shoulder and the absence of relationship to walking distinguish the pain due to these lesions from that of angina pectoris

However the differential diagnosis is often complicated because of the frequent association of disease of the shoulder region and angina pectoris Furthermore the shoulder disturbances are not infrequently the consequence or sequel of a previous acute coronary occlusion (see p 545) Therefore the orthopedic or roentgenologic demonstration of bursitis calcification or periarthritis of the shoulder should not be interpreted as a complete explanation for the patient's pain without a careful clinical history and examination, and a roentgenologic and electrocardiographic study of the heart to determine or exclude the presence of associated angina pectoris and coronary or other cardiac disease

Occasionally pain in the left upper extremity and precordium is due to compression of fibers of the brachial plexus by a *cervical rib* or against the first thoracic rib (*scalenus anterior syndrome*) In the latter syndrome a high fixation of the ribs and sternum or a low position of the shoulder and brachial plexus leads to irritation and stimulation of the plexus with secondary spasm and shortening of the scalenus anterior [7] This causes further elevation of the first rib and compression of the brachial plexus The pain in the precordium and arm is sharp or aching and often radiates to the fourth and fifth fingers It may be associated with numbness, tingling or other paresthesias Relief of the pain by the injection of procaine into the scalenus anterior muscle is helpful in the diagnosis The presence of cervical rib is demonstrated roentgenographically Cure is effected by surgical removal of the cervical rib or by resection of a portion of the scalenus anterior muscle depending on which is the cause of the pain

The *hyperabduction syndrome*, due to constriction of the subclavian artery and brachial plexus is caused by hyperabduction of the arms during sleep or from trauma or postural strain It is characterized by pain in the upper extremity paresthesias and numbness in the hand and fingers

Brachialgia statica paresthetica, occurring only at night and after the patient has gone to sleep is also characterized by pain in the arm and transient paresthesia and is attributed to relaxation of the shoulder girdle during sleep and consequent compression of the subclavian artery and brachial plexus between the clavicle and first rib

PROGNOSIS

The prognosis of angina pectoris is essentially that of the causative underlying disease This is discussed in the individual chapters on coronary artery disease aortic stenosis, syphilitic heart disease etc In general angina pectoris associated with syphilitic heart disease or aortic stenosis has a more serious prognosis than when associated with severe coronary disease Syphilitic aortitis with angina pectoris occurring at night and in the recumbent position has a particularly unfavorable outlook Angina pectoris in cases of *calcific aortic stenosis* is usually a *late symptom*, and the duration of life after its onset is brief The development of angina pectoris in young subjects with rheumatic aortic valvular disease is particularly ominous although occasionally the anginal paroxysms subside In the largest group of cases of angina pectoris, those due to coronary atherosclerosis, the prognosis is more encouraging than in the groups due to the other major causative diseases When there is a definitely remediable contributory factor such as anemia or hyperthyroidism the outlook may be more favorable than in the absence of such factors

Sometimes the cure of a contributing causative factor may lead to the complete disappearance of the paroxysms of angina pectoris

The danger of sudden death is an intrinsic element of the syndrome of angina pectoris and compels a note of caution and reserve in any attempt at predicting the outcome Sudden death occurs in about 10 to 15 per cent of cases in a much larger percentage of cases death is not sudden but unexpected and rapid after a brief manifest attack of myocardial infarction Sudden death is believed to result usually from ventricular fibrillation or cardiac standstill to which the anoxic myocardium or heart with diminished coronary reserve is particularly susceptible However it is not understood why the occurrence of sudden death is not clearly correlated with the frequency or severity of the anginal attacks and it is impossible to prognosticate from either the clinical history or findings which patient with angina pectoris will die suddenly

The advent of angina pectoris does not forebode imminent demise Most patients live for five to ten years after the onset of this symptom Earlier estimates of duration of life averaging four to five years have been revised progressively upward by later studies Of about 500 patients followed by White et al [118] 90 per cent succumbed after an average period of eight years following the onset of symptoms Those still alive had survived for an average interval of 18 4 years A follow up of 1700 cases[109] disclosed an average survival period of 4 6 years for the 679 patients who had died but 32 8 per cent of the males and 34 5 per cent of females were still living after five years and 10 per cent of each sex survived for at least ten years In another follow up study of 6882 cases of angina pectoris for 5 to 23 years[11] about 15 per cent succumbed in the first year after onset thereafter there was an average annual mortality of 9 per cent There was a 5-year survival period of 58 4 per cent compared with a rate of 86 9 per cent for the normal population and a 10 year survival of 37 1 per cent compared to an expected 70 4 per cent Like others[70] I have seen many patients who have survived for more than ten years and occasionally for more than fifteen or twenty years

The hereditary factor sometimes appears important in prognosis A history of angina pectoris and coronary thrombosis in many members of the family especially in the parents with death at an early age bespeaks *an unfavorable and brief course The age of* onset is significant in that the earlier the onset the lower the age at death even when the duration of angina pectoris is relatively long Furthermore when angina pectoris begins in the thirties or forties, it often denotes an hereditary vascular weakness and a likelihood *of early complications and death Pronounced* hypertension or cardiac enlargement previous myocardial infarction and heart failure are among the associated findings which tend to diminish the duration of survival but there are numerous exceptions The association of angina pectoris with diabetes is a very *unfavorable combination*

The progress of cases of angina pectoris may follow any one of many courses Sometimes with or without a significant change in the severity or frequency of the attacks the patient dies suddenly months or years after the initial paroxysm More commonly the course of the disease is punctuated by one or more clinically diagnosed attacks of acute myocardial infarction before death supervenes This occurs in at least 25 per cent of the cases of angina pectoris In some instances there is no positive evidence of an acute myocardial infarction but a sudden sharp increase in the frequency and severity of the anginal paroxysms suggests strongly that a large coronary vessel has become occluded In a large number of cases the clinical course is characterized by the gradual or sometimes sudden development of congestive heart failure usually late in the course of the disease As a rule it may be assumed although this is not always clinically apparent that the failure appeared after the closure of additional coronary vessels and a consequent extension of myocardial damage In still other cases an associated hypertension and diffuse atherosclerosis determines the ultimate outcome the patient eventually succumbs to cerebral thrombosis or embolism cardiac failure or renal insufficiency Finally some patients never develop any serious complications referable to their underlying cardiac disease but die of intercurrent infections carcinoma or other independent disease

Angina pectoris may disappear for long periods of time or permanently even after it has been present for months or years Often this denotes that the living area of myo

cardium which had previously suffered recurrent anoxia and thereupon had engendered pain has finally been destroyed and undergone fibrosis as a result of a complete coronary occlusion Following a clinical attack of acute myocardial infarction the patient may be able to resume moderate activity without recurrence of pain even with exertions that formerly produced it The converse has also been noted i e the onset of angina pectoris following a clinical episode of myocardial infarction Angina pectoris frequently subsides or disappears completely with the development of congestive heart failure or permanent atrial fibrillation This may be explained by the reduction in activity which these complications impose or by the fact that they usually appear after an acute coronary occlusion with death of the pain producing myocardial tissue The disappearance of angina pectoris after correction of anemia has been mentioned

The patient with angina pectoris may be hardly inconvenienced or his activity may be involuntarily so restricted that he is a chronic cardiac invalid Most patients, for at least a few years after the initial episode remain outwardly fairly normal individuals, capable of conducting their business or profession on a somewhat diminished scale of activity, or of earning their livelihood at their usual occupation

TREATMENT

The treatment of angina pectoris is designed primarily to prevent or reduce the frequency of attacks, the paroxysm itself *usually requires no special treatment as it is* brief in duration and subsides spontaneously Occasionally however, specific therapy is indicated to prevent an attack or to relieve pain which occurs frequently even with the patient at rest The prevention of attacks of angina pectoris depends on the treatment of the underlying or contributing causative diseases and the elimination or cure, when possible of the factors which initiate or contribute to the precipitation of the paroxysms

Management of the Underlying Disease

The primary approach in the treatment of any given case should be the determination and proper management of the underlying cause This is discussed under the respective headings, e g , coronary artery disease syphilitic heart disease, aortic valvular disease Measures to improve the basic deficiency in blood supply to the heart are discussed later in this chapter

Treatment and Elimination of Contributing Factors

The administration of liver extract in pernicious or other primary anemias of iron in the iron deficiency anemias or transfusions in anemia due to acute hemorrhage may prevent entirely the occurrence of angina pectoris, even though the basic underlying coronary disease or valvular disease is unaffected In addition it may be necessary to treat the original cause of a secondary anemia when this can be discovered e g , bleeding hemorrhoids peptic ulcer, fibroid uterus or improper diet Similarly, in cases of angina pectoris with hyperthyroidism the latter should be corrected (p 1011)

Although the relation of *disturbances of the gastrointestinal and biliary tract* to angina pectoris is still uncertain their correction may be followed by an amelioration or disappearance of cardiac pain A rigid treatment of peptic ulcer or of functional pylorospasm and gastric hyperchlorhydria by bland frequent feedings alkalis and sedatives, not only relieves the ulcer symptoms but may reduce the frequency of angina pectoris When symptoms are caused by a diaphragmatic hernia they may be controlled by small meal antispasmodics, and the maintenance of the erect position for one half hour or longer postprandially Rarely operative correction is necessary and may also alleviate anginal pain

Cholelithiasis and chronic cholecystitis are *often asymptomatic, especially if the intake is* moderate in amount and bland in quality However, often the severity and persistence of symptoms warrant surgical removal of the gallbladder Cholecystectomy in such cases has been reported as alleviating not only the symptoms referable to the gallbladder but also the anginal symptoms This surgical procedure has been followed in some cases by the disappearance of electrocardiographic abnormalities

The eradication of *foci of infection* such as a diseased tooth or the alleviation of other painful somatic foci to which anginal pain is referred or which help to bring latent painful cardiac impulses to the clinical level, may be followed by a disappearance or diminution of attacks of angina pectoris

Although there is no convincing proof that *tobacco* directly causes angina pectoris except possibly in some sensitive individuals, it is my custom to urge that patients stop smoking when they first consult me for angina pectoris. Statistical studies seem to suggest a significant relationship between smoking and angina pectoris.[81, 43] The mechanism by which tobacco may damage the coronary vessels or heart is not clear. Ordinary and denicotinized cigarettes may have similar effects.[illegible, 9] Often patients feel better generally after foregoing tobacco, even when there is no striking causal relationship between smoking and cardiac pain.

Avoidance of Precipitating Factors

Patients with angina pectoris rapidly learn by themselves to avoid those forms of bodily exertion which are the commonest immediate causes of pain. Usually it is necessary to reduce the distance and especially the speed of walking. To avoid being conspicuous, many patients stop repeatedly in front of stores and pretend they are window shopping. Often the patient may avoid pain by changing his manner of transportation so as to reduce the walking distance to his train or subway. He may have to change his route if it involves walking uphill. Running for buses or trains must be prohibited. The patient must learn to allow sufficient time so that hurrying is unnecessary. Occasionally patients find that if they walk a block until mild pain develops and rest long enough for it to subside, they may then walk moderate distances without discomfort. Walking after meals should be shunned; if essential, the meal should include minimal quantities and the patient should take nitroglycerin prophylactically before walking. I have seen patients whose pain after walking occurred only on their way to the train in the morning. However, by postponing breakfast until they arrived at a restaurant within a block or so of their office, a paroxysm of angina pectoris was evaded. Walking in cold weather, especially against the wind, should be avoided when possible. If feasible, the coldest month or months of the year should be spent in a warm climate.

Other activities which induce pain should be determined by a careful detailed diary kept by the patient. Such studies will teach the patient what he may do and what he should avoid, and will permit the physician to make practical suggestions. Except for walking rapidly or far, many patients will find that they can continue their gainful occupation, sometimes even when this involves certain forms of physical work such as carpentry, painting or plumbing. Sudden and unusual forms of physical exertion and hard physical labor should be interdicted.

Other precipitating factors which should be avoided are discussed below under general measures and include heavy meals, emotional outbursts, prolonged conversation, particularly on the telephone and especially on controversial subjects, straining at stool, and other activities which produce pain in individual patients. Some patients may find relaxation in playing cards, but most experience excessive emotional tension even when the stakes are small. The effect of watching competitive sports or horse racing must be carefully evaluated. Golf is permissible if the patient enjoys it and suffers no pain when playing. Caution should be exercised in the administration of insulin to patients with coronary disease, as hypoglycemia may induce an attack of angina pectoris. Similarly, epinephrine may provoke anginal pain when used diagnostically or in the treatment of bronchial asthma in patients with a diminished coronary reserve.

GENERAL MANAGEMENT

Bed rest is ordinarily not required in the treatment of angina pectoris. However, if a patient consults me promptly after his first attack of angina pectoris, I advise a period of bed rest or great limitation of activity for two weeks, for the sudden development of angina pectoris often denotes the occurrence of an acute coronary occlusion without myocardial infarction. Occasionally attacks of angina pectoris occur so frequently and with such slight bodily exertion that the patient is compelled to rest in bed. The patient should be instructed to summon his physician if the pain persists for more than fifteen minutes or if it is more intense and different from previous attacks. Although those forms of activity which induce attacks should be avoided, it is often possible for the patient to take certain forms of *exercise* or to take them at certain times of the day without discomfort. He should be encouraged to promote this muscular tone and general state of fitness by means of exercise which does not provoke pain or dyspnea.

The *psychologic approach* to the patient with angina pectoris and the *regulation and modification of his work and daily activities* are important elements in his treatment and must be carefully adjusted to individual patients. The layman is often aware that angina pectoris connotes the possibility of sudden death; therefore the term is preferably avoided entirely in a discussion of his disease. The patient's cooperation can usually be obtained if he is informed that the circulation to the heart is impaired. But it is often desirable to explain the patient's exact cardiac status and possible dangers to the patient's nearest relative. At the same time that the patient is made aware of his disability and the necessary modifications in his manner of living, he should also be assured of the probability of a long and useful life if he cooperates in treatment. Many a patient draws extraordinary optimism from the statement that cardiac patients often outlive subjects with a more favorable outlook simply because they lead a more moderate life. It is the physician's task by encouragement and ingenuity to teach the patient to adopt a philosophical attitude to his illness and to accept cheerfully the necessary adjustments in his activity and outlook.

The general questions of *occupation, hours of work, vacations,* etc., must be answered differently in individual cases according to variations in the severity and frequency of the attacks, the patient's station of life, economic status, education and skills, and the character of the underlying disease. In many hospitals, *work classification units* have been set up to aid the cardiac patient in his rehabilitation. These consist of teams of physicians, psychologists, social workers and other pertinent professional personnel who evaluate the patient and help to restore him to gainful employment.[20] Activity and gainful employment must be restricted more in patients with frequent and intractable pain on the slightest exertion than in those with occasional and mild attacks. In those with less severe disease and less frequent attacks, a careful scrutiny and analysis must be made of the patient's work and other daily activities in order to ascertain his capacity for activity and the factors which induce symptoms. His regimen must be adjusted according to the findings.

Long hours, especially when they involve continuous work under tension, must be avoided. Rest periods during the working day, especially after luncheon, are desirable when feasible; if possible also long weekends or a midweekly day of rest should be encouraged. As a rule the patient should retire early and a restful night should be assured, if necessary by the administration of soporifics before retiring or of mild sedatives during the day. In large organizations it is sometimes possible and desirable for the patient to change his job to one which is less trying, even if this transfer entails a moderate reduction in income. Sometimes it is necessary to perform only part time work and in some instances to alter the occupation completely.

Vacations are essential and, if manageable, should be taken at least twice a year. It is advantageous to take vacations during the extremes of hot and cold weather and to choose resorts in climates which avoid these extremes. On the European continent and to lesser extent in this country, patients with angina pectoris were wont to visit various spas both for treatment and for a vacation. While such visits were frequently rewarded by therapeutic benefits, these were due chiefly or entirely to the pleasant surroundings and the surcease from business and domestic stress rather than to any specific curative properties of mineral waters or baths. The well regulated regimen as to diet, exercise, bowel habits and sleep is more likely to be followed in the environment of a spa than at home or even in an ordinary resort. However, the relaxation and change of environment which are usually associated with a vacation in any pleasant surroundings are of sufficient value and are often preferable to a long inconvenient and usually expensive trip to some famous spa. Because of the reduction in oxygen tension at high altitudes, vacations in mountainous regions far above sea level are undesirable, at least theoretically, but I have known patients who have done well at places like Colorado Springs which has an altitude of 7000 feet. Similarly there is a theoretical objection to airplane travel which is usually at 5000 to 10 000 feet, and especially to stratospheric or substratospheric flying in transcontinental trips, but most commercial planes are adequately pressurized; if not, oxygen should be used when flights are made at heights exceeding 7500 feet, but especially above 10 000 feet. Most patients with angina pectoris tolerate usual commercial flights.

Diet There is no specific dietary treatment for patients with angina pectoris except a low fat diet designed to inhibit an underlying coronary atherosclerosis. The diet often depends on associated factors. In general a low calorie diet is desirable especially if the patient is overweight. It is particularly advisable to divide the dietary intake into small meals which may be taken more frequently than the usual three times daily. In the presence of associated biliary tract disease or a peptic ulcer appropriate dietary measures should be instituted. Functional gastrointestinal disturbances characterized by flatulence, postprandial distention and gaseous eructation should be treated by a bland diet (low in roughage, elimination of raw fruits, fried foods, gravies, pastries, cabbage, onions, corn and other gas producing vegetables).

Bowels Regularity of bowel habit always desirable is particularly important in these patients for colonic stasis and associated flatulence often help to produce attacks. Mild laxatives may be given if necessary. Excessive straining at stool should be avoided.

Tobacco (p 477)

Coffee and Tea These may be taken in moderate quantities. They have the theoretical advantage of being coronary vasodilators and the disadvantage of provoking nervousness and sleeplessness in some patients.

Alcohol (see drug therapy below)

DRUG THERAPY

Nitrites

The nitrites which cause direct coronary vasodilatation and increase the coronary flow more than the work of the heart[66] represent the only specific medication in the relief of angina pectoris. As a rule they are used for prompt relief of the pain after the attack develops but they should also be employed prophylactically. For the latter purpose they are taken before such activities as are known by experience to produce pain. Of course whenever possible it is best to avoid both the precipitating factor which causes pain and the nitrites. Under no circumstances should the nitrites be taken to permit the patient to perform some unusual strenuous activity which is likely to cause harm.

Nitroglycerin is the drug of choice since it is cheap, convenient to take and next to amyl nitrite acts most rapidly. It is administered in tablets which the patient is instructed to dissolve under the tongue. If the tablets are not readily soluble they may be inert or their action delayed. The usual therapeutic dose is 1/100 grain but it is preferable to begin with a 1/200 grain tablet which often suffices and is less likely to induce uncomfortable side actions. Its action is noticeable in one to two minutes and continues for fifteen minutes to an hour. In most cases the relief is striking as well as prompt. Often however it may be accompanied by mild fullness, warmth or throbbing in the head. Rarely in subjects with an idiosyncrasy to the drug severe headache, faintness or even syncope may occur. Until the effects of the drug are known it is advisable for the patient to sit down or find some support when he takes nitroglycerin. If after the repeated beneficial use of nitroglycerin the patient suffers an attack of pain which does not respond to this therapy he should be instructed to cease all activity at once and call his physician. Except when it is used prophylactically nitroglycerin should not be taken for those attacks which are known to subside promptly with a brief period of rest. Since the pain will disappear rapidly and spontaneously there is no need for the patient to suffer any unpleasant side actions of the drug. Russek et al[91] reported a paradoxical unfavorable effect of nitroglycerin with respect to the exercise electrocardiogram in 10 per cent of 158 patients with coronary disease and Starr et al[104] occasionally observed a similar unfavorable effect on the ballistocardiogram. I have observed nothing of this kind with respect to its effect on clinical symptoms.

Nitroglycerin has also been made available in a sustained action tablet termed *nitroglyn* for oral (not sublingual) use containing 1/25 or 1/10 grain and designed to be released uniformly for a period of 10 to 12 hours. A tablet at breakfast and bedtime is said to prevent or greatly diminish attacks of angina pectoris. In contrast to the unequivocal effectiveness of sublingually administered nitroglycerin, Nitroglyn is inconstantly effective but the drug in 1/10 grain dosage appears to be beneficial in some patients.

Amyl nitrite introduced by Lauder Brunton[15] in 1867 acts more rapidly (in ten to fifteen seconds) but its action lasts only for several minutes. It is administered in small glass pearls or ampules which must be

crushed in a handkerchief and inhaled Its disadvantages are its expense, inconvenience in carrying and administration and the distinctive odor which calls undesired attention to the patient when it is taken in the presence of others Its unpleasant side actions are similar to those of nitroglycerin

Other nitrites are rarely used or indicated *Sodium nitrite* administered orally in tablet form, in doses of 0 03 to 0 06 gram (½ to 1 grain) requires ten to fifteen minutes for an effect which continues for an hour or longer

Long Acting Nitrates Long acting nitrates are designed to provide the coronary vasodilator effect of the nitrites but for a prolonged sustained period When these drugs are given throughout the day it is hoped that anginal attacks can be prevented or at least reduced in number and severity The action of these nitrates is dependent on the continued release of nitrites *Erythrol tetranitrate*, which may be given orally as tablets in doses of 0 015 to 0 030 gram (¼ to ½ grain) requires fifteen minutes for effect, the duration of which is several hours Similarly *mannitol hexanitrate* and *mannitol pentanitrate*, the action of which is even more delayed and prolonged may be given in ¼ to ½ grain doses for prophylactic effect

Peritrate (pentaerythritol tetranitrate) is a long acting nitrate available in 10 mg tablets, and is administered in doses of one or two tablets three or four times daily The prophylactic action is said to begin 1½ hours after a dose and to last 4 to 5 hours It is contraindicated in glaucoma as are all the other nitrates Side effects include occasional headache and nausea which may disappear after continued administration weakness, palpitation flushing and mild hypotension Rarely a dermatitis results from drug intolerance

Very favorable claims have been made for this long acting nitrate Among 258 patients treated by Dailheu Geoffroy[22] with 60 mg daily in divided doses over 80 per cent showed a good result in contrast with only 33 per cent improvement with other coronary vasodilators Winsor and Humphreys[121] reported that Peritrate in an average daily dosage of 30 mg (range 10 to 60 mg) reduced attacks of angina pectoris in 125 patients by an average of 78 4 per cent whereas no reduction in the number of attacks was effected in 125 patients used as controls and given placebos, aminophylline (6 gm daily orally), khellin (60 mg daily) or Theocalcin (1 5 gm daily) In addition, Peritrate was said to reduce significantly the requirement for nitroglycerin, increase exercise tolerance and like nitroglycerin, reduce or prevent the electrocardiographic RS T depressions induced by exercise[90, 93] Similar favorable observations were reported by other investigators but it is of importance to note that few, if any, patients who required nitroglycerin were able to dispense with its use entirely by taking Peritrate

Despite these optimistic reports, I have not found that Peritrate (or other long acting nitrate compounds) is a valuable addition to the therapy of angina pectoris, or that it has given sufficiently consistent benefit to justify its recommendation Recently Kalman on et al,[50] using the double blind method failed to demonstrate any beneficial effects of Peritrate on angina pectoris in 23 patients The variable course of angina pectoris, the spontaneous variations in the number of attacks and in the physiologic and environmental factors which precipitate them, and especially the importance of emotional influences render evaluation of drug therapy extremely difficult in angina pectoris Therefore, unless the effectiveness of a drug is unequivocal like that of nitroglycerin, or unless it can eliminate the need for nitroglycerin it is probably of little or no value in controlling the attacks of pain

Triethanolamine trinitrate (Methamine), administered in doses of 2 mg four times daily, was reported to benefit patients with angina pectoris but Friend et al[35] found this drug to be no better than a placebo, as has been my own experience

Xanthines

Members of the xanthine group of drugs, usually compounds of theobromine or theophylline have been widely employed in cases of angina pectoris due to coronary disease despite considerable doubt as to their clinical effectiveness Their use is based on experimental observations indicating that these drugs produce coronary vasodilatation and an increased coronary flow in isolated perfused hearts heart-lung preparations or in the intact animal However, when the dosage of drug administered and the amount and transiency of increased flow are considered it is questionable whether these experimental

observations form an adequate basis for anticipating clinical benefit in human cases of angina pectoris Controlled studies in patients with angina pectoris have not confirmed the claims of clinical benefit from the xanthine drugs in angina pectoris I have virtually discontinued their use for angina pectoris except in a few patients who are convinced of their value

Aminophylline is used most frequently but its absorption is poor or inconstant when administered orally and gastrointestinal distress is caused with adequate dosage Recently choline theophyllinate, in doses of 0 2 to 1 0 gm four times daily has been reported to give relief and to control the anginal syndrome in 29 of 32 patients with angina pectoris[4] This preparation was said to be better absorbed and give higher blood levels than equivalent amounts of aminophylline and yet nausea or diarrhea occurred in only 7 3 per cent of the cases A highly favorable report of the effectiveness of choline theophyllinate was made also by Aravanis[2] Despite these favorable reports the value of the drug requires further confirmation before it can be recommended Other xanthine derivatives used and their dosage include

- Theobromine and sodium acetate—0 5 to 1 0 gm four times daily
- Theocalcin (theobromine-calcium salicylate)—0 5 to 1 0 gm four times daily
- Aminophylline (theophylline ethylenediamine)—0 1 to 0 2 gm three or four times daily

Many of the xanthine drugs have been marketed in combination with sedatives usually with phenobarbital The chief disadvantage is the rigidity imposed on the relative dosage of the two components in particular the dose of phenobarbital often needs to be altered for different patients and even for the same patient at different times The advantage is that the sedative may assure the benefit of at least one drug in the combination

Sedatives

Sedatives are among the most widely prescribed drugs in the treatment of angina pectoris Their purpose is to allay anxiety and minimize the emotional reactions which may precipitate attacks of pain *Phenobarbital* in doses of 0 015 to 0 03 gm (¼ to ½ grain) three times daily is employed most frequently sometimes in combination with a xanthine derivative *Bromides* in doses of 0 3 to 1 0 gm (5 to 15 grains) and *chloral hydrate* in 0 3 gm (5 grain) doses alone or in combination three times daily are among other sedatives often administered It is often necessary to prescribe soporifics for sleeplessness e g Seconal 0 1 to 0 2 gm (1½ to 3 grains), Nembutal 1½ to 3 grains, or Veronal 0 3 to 0 6 gm (5 to 10 grains) on retiring Opiates are not indicated in the treatment of angina pectoris because the recurrence of attacks would tend to lead to addiction If pain is persistent and unrelieved by nitrites the probability of myocardial infarction or some other cause should be considered

Recently the so-called *ataractic or tranquilizing drugs* have been administered instead of the established sedatives Miltown or Equanil in doses of 200 to 400 mg three times daily or reserpine 0 25 mg one to three times daily has been most commonly employed Their benefit in angina pectoris applies only indirectly insofar as they serve to reduce emotional tension See also chlorpromazine (Thorazine) on page 489

Other Drugs

Alcohol is often prescribed in ½ to 1 oz doses both for the prevention and relief of attacks It is the oldest drug used for this purpose since its benefits were mentioned in Heberden s original description It is doubtful that alcohol has any direct value in the prevention or alleviation of the anginal paroxysms[103] However in dogs production of a blood alcohol level comparable to that which is present in man after consuming two or three cocktails caused marked increases in coronary arterial inflow and coronary sinus outflow[54] Although I always permit and sometimes advise the ingestion of moderate amounts of alcohol by patients with angina pectoris especially elderly patients I do so more for its beneficial effect on general well being than for any dramatic improvement in the angina pectoris itself On the other hand I have seen many patients who have been made worse by an overenthusiastic indulgence in alcohol This applies particularly to patients with peptic ulcer irritable spastic colon or other gastrointestinal disturbance and those with symptoms of prostatic obstruction

Trichlorethylene has been employed for the relief and prevention of attacks of angina pectoris[63] It is administered by inhalation

three inhalations being taken after crushing a glass ampule containing 1 cc of the drug. Any beneficial effect is not dependent on coronary vasodilatation but on its anesthetic, analgesic or sedative action. Occasionally it may cause a brief loss of consciousness.

Digitalis is not indicated in the treatment of angina pectoris unless heart failure or atrial fibrillation is present. Some of the nocturnal attacks of angina pectoris occurring when the patient is recumbent, are due in part or entirely to left ventricular failure. These may be alleviated by digitalization, rigid sodium restriction, the administration of aminophylline 0.25 gm. intravenously or 0.5 gm. by rectal suppository before the patient retires, and by the use of mercurial diuretics.

Heparin has been reported to have a startlingly beneficial effect on angina pectoris[37] (see p. 422 for effect of heparin on serum lipids). According to Graham et al.[37] when heparin was given once or twice weekly in doses of 50 to 100 mg. intravenously or intramuscularly, there was a marked reduction in the number of attacks of angina pectoris in 55 of 59 patients. In my experience the administration of heparin sodium according to the same dosage schedule has not been of significant benefit in the control of anginal pain even though occasional patients reported improvement. Most recent reports indicate that heparin is not a useful therapeutic agent in angina pectoris.[8, 35, 41, 53]

Quinidine has been suggested as a therapeutic agent in the treatment of angina pectoris and Riseman et al.[86] found that quinine sulfate in doses of 0.3 to 0.4 gm. every 8 hours, is the drug of choice when the cinchona alkaloids are used in the treatment of angina pectoris. I have not found them of value. Proger and his associates[79] reported that quinidine exerted a beneficial effect on angina pectoris when attacks were precipitated or increased in frequency by a cardiac irregularity.

Papaverine has been recommended in oral doses of 0.1 gm. four times daily on the basis of its coronary vasodilator effect in animals and its sedative action.[27] However, reevaluation of the drug in doses up to 300 mg. by some of its early advocates, using new groups of patients, failed to disclose any benefit in angina pectoris.[102] These conflicting reports by the same observers form an important commentary on the evaluation of drugs in angina pectoris.

Dioxylene phosphate (Paveril phosphate) is a synthetic preparation related to papaverine with a similar action in relaxing smooth muscle and promoting coronary flow, but with less toxicity. Despite reports by a number of observers of clinical improvement in patients with angina pectoris[65, 88] when the drug was given in doses of 0.2 to 0.4 gm., I have found Paveril to be of no significant value and no longer use it. Nausea, abdominal cramps, dizziness, sweating and flushing, although relatively mild, were among some of the complaints of patients receiving the medication.

Ethaverine (diquinol), like dioxylene phosphate, is an analogue of papaverine which has the advantage of a slower onset and more prolonged action in dilating the coronary arteries in dogs. However, its administration to patients with angina pectoris in doses of 400 mg. was no more effective than that of lactose[1] or other placebos.[103]

Khellin, an extract of seeds from an Eastern Mediterranean plant, long used as an antispasmodic for ureteral colic, was recently found to be a potent bronchodilator and coronary vasodilator. Favorable results in the treatment of angina pectoris were first reported when the drug was injected intramuscularly in 100 mg. doses or given orally in 50 to 100 mg. doses three times daily.[1]

Khellin is available in 20 mg. and 40 mg. enteric coated tablets (Ammivin, Eskel, Visammin) for oral use, and has been recommended in initial doses of 20 or 40 mg. per day. This was increased each week by a daily increment of 20 or 40 mg. so long as no unpleasant side effects occurred. Otherwise the dosage was decreased or the drug withdrawn for two or three days and reinstituted at a lower dosage level. Daily doses of 200 mg. have been given, but even 50 to 100 mg. daily is not usually well tolerated. Often after a therapeutic effect only maintenance doses of 20 to 40 mg. daily were administered.

Reports in this country indicated that Visammin (khellin) effected a good or excellent therapeutic response in 35 to 90 per cent of cases of angina pectoris.[73, 90] The most common side effects are anorexia, nervousness, nausea, dizziness, weakness and depression but also vertigo, headache, diarrhea and insomnia. In my experience khellin was either ineffective in the treatment of angina

pectoris in all but occasional patients or it was impossible to give it in high enough dosage without eliciting intolerable side-effects Despite numerous previous favorable reports Greiner and associates[52] and Hultgren and associates[43] who made a study for the Council on Pharmacy of the American Medical Association found that khellin did not have any significant value in the treatment of angina pectoris It is possible that some of the favorable reports indicating a reduction in attacks of angina pectoris with khellin were due to the toxicity of the drug which necessitated limitation of activity or even bed rest Time and usage have apparently convinced the practicing physician of the ineffectiveness of khellin because I now rarely hear of its use

Testosterone Favorable results have been reported by a number of observers[57] but not by Levine and Likoff[53] In the light of recent studies of the effect of gonadal hormones on lipid metabolism (p 427) there is a theoretical contraindication to the use of androgens

The claims that vitamin E (alpha tocopherol) has therapeutic merit in cases of angina pectoris and other forms of heart disease have not been confirmed[54] This applies also to claims for tetraethylammonium chloride (TEAC) administered intramuscularly[46]

The iodides are still widely prescribed for angina pectoris but except in cases due to syphilitic ostial stenosis there is no sound basis for their usefulness in this condition Epinephrine ephedrine and other sympathomimetic drugs should not be given

Physiotherapy and balneotherapy have been used in the treatment of angina pectoris especially at various spas There is no acceptable evidence of their specific value or of the value of diathermy to the chest wall Roentgen ray therapy to the adrenals has been used to diminish acute discharges of epinephrine ■ There is insufficient evidence to recommend its employment

INDUCED MYXEDEMA BY THIOURACIL OR RADIOIODINE

Antithyroid drugs (thiourea derivatives) have been administered in order to reduce the patient's metabolism and thereby diminish the work of the heart and its need for coronary blood flow Numerous reports have appeared of improvement in persons with angina pectoris following the use of thiouracil[60] propylthiouracil[112] and methylthiouracil The disadvantages of these drugs including toxicity need for close supervision and prolonged treatment and temporary effect have also been documented

Radioiodine

The desired degree of hypothyroidism is more satisfactorily attained by the aid of radioactive iodine (I^{131}) Usually three oral doses each 20 millicuries or less are given at weekly intervals Thereafter additional single doses are given at one- to two-month intervals until hypothyroidism is manifest within two to six months after initiating treatment

Favorable results in the treatment of angina pectoris with I^{131} have been reported by Blumgart and associates[4] Wolferth et al[3] and Jaffe et al[44] and others Jaffe et al reported excellent results in 56 per cent and good results in 37 per cent of 94 patients with angina pectoris treated with radioactive iodine Blumgart et al presented the results of I^{131} treatment of 1070 euthyroid patients with advanced cardiac disease including 87 of their own and 983 reported through the cooperation of 49 other clinics Approximately 75 per cent of 720 of these patients with angina pectoris showed worth while improvement (half showed marked improvement and half a good result) The best results appeared to be obtained when the disease was relatively stable or only slightly progressive On the other hand I^{131} treatment was regarded as contraindicated when there was a recent onset of angina pectoris status anginosus or other evidence of rapidly progressive cardiovascular disease although practice in this regard is not uniform in all clinics Small daily doses (6–30 mg) of thyroid were usually administered after the I^{131} to maintain the lowest metabolic rate consistent with comfort usually minus 20 to minus 25 per cent

I have observed a number of impressive results in both patients with angina pectoris and those with severe left ventricular failure but chiefly the former Nevertheless I am skeptical that the procedure is consistently effective and that the reported benefits can be credited to the postulated rationale of the treatment Probably as with reported benefits to angina pectoris from a variety of drugs and operative procedures the results following radioiodine treatment are due to better

collateral management of the patient, enthusiasm and encouragement of the investigator, psychic factors concerned in angina pectoris, and to the variable course of the disease itself independent of treatment

The production of myxedema even when controlled by the use of thyroid extract, must be regarded as a drastic measure in the treatment of angina pectoris and can only be justified in so called intractable angina pectoris after all other medical measures and patience have been exhausted This denotes that it will be indicated in only occasional instances The simplicity of the treatment and the absence of dangerous complications render it preferable to surgical operations in these cases Furthermore, it can be made available to patients with angina pectoris and heart failure as well as other very ill patients who would be too poor risks for the surgical procedures

PARAVERTEBRAL ALCOHOL INJECTIONS

In a small percentage of cases of angina pectoris the attacks recur with such frequency and the relief from multiple daily doses of the nitrites is so transient and incomplete that it is sometimes necessary to resort to opiates For such cases, excellent results have sometimes been obtained by paravertebral alcohol injections which block the painful impulses from the heart However, the disadvantages of this treatment and the availability of other forms of therapy for intractable angina pectoris have cast the procedure of paravertebral alcohol block into relative disuse

The points at which anesthesia is effected are the upper five or six thoracic sympathetic ganglia and their adjacent rami communicantes through which the painful impulses eventually pass (see p 450) In some patients referred pains may still be experienced in the region of the ear and lower jaw and these may be abolished by injection of the mandibular nerve [6]

Satisfactory results have been reported by Levy and Moore[60] in 15 patients and by J C White and Bland[117] in 75 patients Good results with virtually complete relief of pain were obtained in 56 per cent of the latter series, a reduction in the severity of pain in 21 per cent and no appreciable result in 8 per cent Although many of these patients were extremely ill there was a mortality of only 8 per cent within two weeks of the procedure In 40 cases there was no recurrence for periods up to nine years but in 14 pain reappeared within two and one half months to five years

The advantage of the procedure is the ability to perform it without a general anesthetic and with minimal discomfort to the patient and only slight risk However, there is need for practice and skill, in 10 to 20 per cent of the attempts, a successful nerve block is not obtained The most common complication is a painful intercostal neuritis due to the alcohol injected It usually clears in a few months but may be more persistent and so severe that the posterior nerve roots must be sectioned Occasionally there is accidental injury to the pleura with consequent pleuritis pleural effusion or pneumothorax and rarely injury to the spinal cord structures

The *technique of paravertebral alcohol injection* as described by White and Smithwick[118] and by Levy and Moore[60] is as follows

The patient is given a sedative the night before and on the morning of the injection also 1/100 grain of atropine is administered hypodermically to exclude vagovagal reflexes The patient is injected in his own bed while lying on the side opposite that to be injected His knees are drawn up and his head bent forward and supported by a pillow as for a spinal tap The highest prominent vertebral spine is the seventh cervical vertebra This and the spinous processes below down to the fifth thoracic, are the bony landmarks Each of these spinous processes is at the same horizontal level as the transverse process and angle of the rib below The injections are made from 3 5 to 4 cm lateral to the spinous process on the side of the pain at the levels of the seventh cervical and upper four dorsal spines

By means of a fine hypodermic needle intracutaneous wheals are made at the sites of injection Then needles 10 cm long are inserted through these wheals perpendicular to the surface of the back and at a depth of 3 to 3 5 cm until they touch the upper four transverse processes or the articulating portion of the ribs These needles should be made of rustless flexible steel thin lumbar puncture needles or special Labat needles may be used Markers of narrow rubber tubing are placed on the needles in order to measure the depth to which the needles are inserted Having been inserted to the point mentioned the needles are then inclined slightly caudally so as to touch the lower border of the transverse process or angle of the rib The depth marker is then pulled up so as to be 3 cm from the skin The needle is directed medially at an angle of 20 and inserted 3 cm until it is felt in contact with the lateral surface of the body of the vertebra If contact is made at a lesser depth the needle should be directed less medially The total depth of insertion through the skin varies from 5 to

6 cm in thin persons to [illegible] to 10 cm in patients with a thick chest wall

After insertion of the needles aspiration is performed to exclude the possibility that the needle may have entered a blood vessel or the subarachnoid space If this occurs the needle is withdrawn and its direction altered When the needles are properly placed [illegible] cc of 2 per cent procain is injected through each Within ten minutes anesthesia should be effected in the axilla the inner surface of the arm and over the third and fourth ribs anteriorly and posteriorly A Horner s syndrome and anhydrosis of the arm and side of the head and neck usually appear with proper anesthesia The hand and usually the neck and face feel hot and dry When this preliminary anesthesia has been accomplished an additional 3 cc of 1 per cent procain is injected at each site to prevent pain from the subsequent injection of alcohol Finally 5 cc of 95 per cent alcohol is injected slowly through each needle withdrawing the plunger of the injecting syringe each 0 5 cc in order to be certain that the needle has not slipped into a blood vessel or subarachnoid space The patient is kept quiet for one hour lying on his side with his back supported by pillows He is usually out of bed the following day if hospitalized for the procedure he may leave in 72 hours

SURGICAL TREATMENT OF ANGINA PECTORIS

The various surgical procedures advocated for the treatment of angina pectoris were designed either (a) to interrupt painful impulses by cutting sensory fibers in the sympathetics or their attachments to the spinal cord (b) to diminish the work of the heart by total thyroidectomy or (c) to promote the development of a collateral circulation to the heart

Resection of Pain Fibers

Earlier operations on the cervical sympathetic chain or ganglia or stellate ganglia gave inconsistent results because they only partially interrupted the sensory pain fibers from the heart Based on the knowledge that all painful impulses from the heart eventually pass through the upper four or five thoracic ganglia their rami communicantes and the corresponding thoracic posterior spinal nerve roots successful results in relieving angina pectoris have been obtained either by (a) surgical excision of the upper four or five thoracic sympathetic ganglia or (b) section of the upper four or five dorsal roots (posterior rhizotomy)

White and Bland[117] reported satisfactory relief with the former procedure in 8 cases with one death Landgren and Olivecrona[63] reported a series of 71 patients in whom stellate ganglionectomy and the removal of the upper three or four thoracic ganglia was performed for angina pectoris with complete relief in 44 per cent substantial relief in an additional 41 per cent unsatisfactory result in 7 per cent and 6 deaths within one month of the operation Pain in the neck or jaw was not relieved Occasionally there was a postoperative pain in the arm ("traumatic neuritis") which usually was mild but in one case required a posterior root section for relief Evans and Poppen[9] reported satisfactory results in 13 of 16 patients with angina pectoris following *bilateral* resection of the first to fourth dorsal ganglia Among the side effects of the operation are a Horner s syndrome swelling of the nasal mucosa and occasional postural hypotension

In cases with bilateral pain a posterior rhizotomy may be preferable because the dorsal posterior roots on both sides can be sectioned at a single operation This is a more formidable operation than ganglionectomy because an extensive laminectomy must be performed Both types of operations are rarely indicated

Total Thyroidectomy

The operation of total thyroidectomy was designed to ameliorate angina pectoris by diminishing the work of the heart and for other theoretical reasons and some satisfactory results were reported However it has virtually been abandoned When considered desirable myxedema may be induced more simply by the administration of radioiodine (p 483)

Production of a Collateral Blood Supply to the Heart

Several procedures have been used

(1) Grafts of intercostal muscle[6] of omentum[78] of lung[23] or of jejunum[57] have been sutured to the heart in the hope that extracardiac vessels in these structures would form functioning collateral channels to the heart These procedures are ineffective and either have been abandoned or have not gained acceptance

(2) *Cardiopericardiopexy* Pericardial adhesions have been produced by irritants to the epicardium[67] or by talc (powdered silica) instilled into the pericardial cavity (Thompson[109]) These procedures are designed to create a sterile granulomatous pericarditis and thus to promote pericardial vascular anastomoses with the coronary arteries Thus it is claimed that attacks of angina pectoris are prevented or diminished in frequency

and exercise tolerance enhanced Autopsies on patients who died ten years or more after the procedures were reported to show that the granulomas provoked by the silica powder remained vascular [77] However it is highly improbable that the fine vascular channels were of any functional importance

A small anterior incision is made over the left fifth costal cartilage, which is excised the pericardial sac is opened and all the pericardial fluid is removed The surface of the heart is completely covered by magnesium silicate powder (using 2 to 6 teaspoonfuls by volume or 4 to 12 gm by weight) Scarification or scraping of the epicardium is unnecessary

In the so called *Beck I operation*[6, 66] there is a combination of (a) abrasion of the epicardium and lining of the parietal pericardium (b) application of an irritant, 0 2 gm of powdered asbestos, to these surfaces, (c) partial occlusion of the coronary sinus where it enters the right atrium and (d) grafting of the parietal pericardium and mediastinal fat to the surface of the heart

De epicardialization is a related surgical procedure designed to relieve angina pectoris by promoting a collateral circulation [45] The application of 95 per cent phenol to the dog's epicardium was found to permit the development of anastomoses between the pericardial and coronary vessels which were large enough to carry the Schlesinger lead agar injection mass, i e, vessels 40 micra or more in diameter In 18 patients with intractable angina pectoris, an operation consisting of phenolization, instillation of talc and pneumopexy has resulted in complete relief of pain in 14 without any operative deaths

The operative mortality in the Thompson procedure is 12 per cent, but this includes operations on very sick, completely incapacitated individuals [108, 77] Pericardial effusion pleural effusion, pneumonitis and atelectasis are common postoperative occurrences Fever persists one or two weeks According to criteria set up by Thompson and Plachta,[108] there was a 50 per cent improvement in 90 per cent and a 75 per cent improvement in 40 per cent of the operated patients In this latter group the patients required no medication and no restriction of physical activity after recovery from the operative procedure In another group of 36 patients subjected to talc cardiopericardiopexy the results were interpreted as excellent in 14, good in 12 [1] The immediate operative mortality was 5 5 per cent (2 patients) and another two patients died of non cardiac causes in the follow up period The average hospital stay was 10 to 14 days Of 33 patients who had the Beck I operation there was no anginal pain in 36 3 per cent and less pain in 48 5 per cent, for a total of 84 8 per cent 27 2 per cent were better able to work without limitations and 51 4 per cent with some limitations, for a total of 78 6 per cent [6, 14] The immediate postoperative mortality rate of about 7 per cent has decreased considerably with experience

(3) Ligation of the great cardiac vein with or without pericoronary neurectomy[30, 31] has been performed This was based on observations that preliminary ligation of the coronary sinus in dogs greatly diminishes the incidence of death or myocardial infarction after subsequent experimental ligation of a coronary artery [29] This procedure has given way to the other operations discussed in this section

(4) *Beck Operation II* [6, 31, 14] In the first stage operation a vein graft is placed between the aorta and coronary sinus for the purpose of shunting arterial blood After an interval of two or three weeks, at the second stage procedure, the coronary sinus is partially occluded in order to raise the pressure in that vessel This is designed to cause the arterialized blood entering the sinus from the aorta to flow retrograde, back to the coronary capillaries Experimental observations in dogs indicated that this operation was effective, when a major coronary occlusion was later induced in reducing fatalities in preventing myocardial infarction or in diminishing the size of an infarct However, subsequent studies[26, 2] indicate that retroperfusion of the capillary bed persists only for about five weeks, after which the vein becomes occluded and loses functional contact with the capillary bed In view of this finding the beneficial effect of the operation is now attributed to the early development and persistence of functioning intercoronary collaterals which may have been produced by myocardial anoxia caused by the operation [65] The Beck II operation is being performed less frequently because of the special skill and training required the need for two operations the relatively high operative mortality (26%) and the

occasional development of congestive heart failure due to the fistula

(5) *Implantation of Internal Mammary Artery into Myocardium*[112] Vineberg implanted the internal mammary artery with an open freely bleeding intercostal branch directly into the left ventricular myocardium the artery being pulled into a myocardial tunnel after blunt dissection between the muscle bundles Pericardial fat pads used as grafts were applied to the surface of the left ventricle to supplement internal mammary artery implantation It was claimed that the implanted artery sent out large branches to the ventricular myocardium in over 70 per cent of experimental animals and that these branches were large enough to carry a supply of arterial blood into the heart at a rate as high as 51 cc per minute The presence of patent anastomoses between the implanted artery and the coronary arterial branches was confirmed by Glenn et al [36] but the new vessels were small resembling granulation tissue and tended to disappear at the end of eight weeks After four years experience with this operative procedure in the treatment of 29 patients with coronary artery insufficiency Vineberg et al [11] reported that about 70 per cent of the patients were greatly improved and returned to work The mortality rate was 4 3 per cent among patients with angina pectoris at rest

Evaluation of Surgical Revascularization of the Heart

Despite the claims made for the various operative procedures their value for the treatment of angina pectoris or other forms of coronary heart disease has not been established The results improve according to (or because of) the degree of enthusiasm of the surgeon or the medical collaborator Nevertheless many patients claim to have experienced considerable improvement after these operations and it is sometimes necessary to subject patients to them For the present I consent to trial of the coronary operations only for patients with intractable angina pectoris and only after all forms of medical therapy have been exhausted It has not been recommended as a protection against further myocardial infarction in patients with more than one coronary occlusion Heart failure is regarded as a contraindication It has seemed to me that among the patients who have reported benefit the anginal or associated pain and disability were often or usually atypical in many respects and that emotional factors were especially important The Thompson the Beck I and the Vineberg procedures are the ones most frequently performed currently

It has not been satisfactorily demonstrated that these current surgical procedures actually increase the blood supply to the heart by the collateral circulation which the operations are designed to create Direct observations on hearts so operated fail to show that the induced pericardial vessels the venous graft or the implanted mammary artery are of significant size or persist long enough to be of functional importance The cardiopericardial vessels induced by silica powder are puny and do not even compare with the substantial intercoronary vessels already present in the heart with significant coronary heart disease The vessels formed after internal mammary implantation are both unimpressive in size and usually insignificant or occluded after eight weeks The Beck I procedure accomplishes little if anything more than the Thompson silica operation In the Beck II operation the graft does not remain patent or does not maintain contact with the coronary bed after about five weeks

Thus any benefit that may accrue from these operations is due to better preoperative or postoperative medical care to the psychic influence of an operative procedure and the promise and enthusiasm accompanying it or to some factor in the operation which is not understood but not directly due to the new collateral circulation That the operative procedure may result in myocardial anoxia sufficient to induce intercoronary anastomoses [6] similar to those which follow coronary occlusion[13 14] has been mentioned The possibility that the interruption of nerve pathways may be concerned in the mechanism of chest pain must also be considered

In the absence of direct demonstration that functionally significant collateral vessels are produced by these operations the evidence purported to show their beneficial influence in patients with coronary insufficiency is unconvincing Experiments have been reported which were said to demonstrate that the prophylactic performance of one of these operations reduced the mortality

rate and prevented myocardial infarction or diminished the size of the infarct following a subsequently induced coronary occlusion in dogs These observations are difficult to evaluate because the results have been variable and contradictory and depend in large measure on the exact site of coronary occlusion and on the relatively frequent presence of large anastomoses between the major coronary arteries in the dog Burchell[18] demonstrated that all the coronary arteries in the dog could be gradually occluded without the development of myocardial infarction even though no protective operation had been performed previously to increase the coronary blood flow Other experimental evidence of the benefit of these operations consists in the demonstration of a backflow from the cannulated distal end of a ligated and cut coronary artery[illegible] Such evidence has been likewise contradictory and not directly applicable to the possible value of these operations in human coronary heart disease In humans with severe angina pectoris, coronary occlusions with intercoronary anastomoses are already present[18] and the value of the added operation is questionable Finally in humans *evidence of benefit is indirect and consists of* reported relief or diminution of pain and increased functional capacity Because of the psychic and subjective factors involved in these criteria, they are notably subject to error and bias Evidence of increased survival after the operations is even more difficult to evaluate because of our incomplete knowledge and the variable nature of the course of angina pectoris

Selective Vagotomy

Because neurogenic factors appear to be concerned in the occurrence of angina pectoris, Scherlis and Cowley[44] studied the advisability of eliminating vagal coronary vasoconstrictive impulses In anesthetized open chest dogs, stimulation of cardiac branches of the left thoracic vagus nerve produced electrocardiographic changes resembling those of acute "through-and through" myocardial infarction, whereas stimulation of the stellate ganglion caused S-T depressions suggestive of subendocardial myocardial ischemia In 4 patients with severe angina pectoris not relieved by accepted medical therapy section of the vagal cardiac branches resulted in great improvement in three and slight improvement in the fourth patient

MANAGEMENT OF ACUTE ANGINA PECTORIS STATUS ANGINOSUS ANGINA DECUBITUS INTRACTABLE ANGINA PECTORIS

In many patients the status of angina pectoris remains fairly stabilized, variations in the frequency and severity of the attacks of pain depending on similar variations in environmental and physiologic factors, such as the degree of physical activity, climatic conditions, intake of food, emotional states and the like One may then regard the organic factors (coronary disease aortic valvular disease, and so on) which are responsible for the diminished coronary reserve as fairly stable, whereas the physiologic disturbances which strain the cardiac reserve vary in frequency and degree, but are usually transient From time to time there is an acute "coronary" disturbance during which the character of the anginal syndrome is altered The attack of pain may be more prolonged and more severe, it may occur at rest and without obvious cause whereas previously there was an apparent precipitating factor, it may occur particularly when the patient is recumbent with more or less relief on sitting or standing (angina decubitus), it may occur more frequently and with less and less provocation, rest and/or nitroglycerin may afford little or no relief or the relief may be of minimal duration (status anginosus intractable angina)

Under these varied circumstances a search must be made carefully for some physiologic or emotional change that could possibly account for the altered clinical state As a rule however the cause is an organic factor which further diminishes or eliminates the coronary reserve or rarely an organic stress such as hyperthyroidism which cannot be handled by the preexisting subnormal coronary reserve A common but usually easily recognized organic factor which further reduces the coronary reserve and alters the status of angina pectoris, is an acute coronary occlusion with myocardial infarction Its treatment is discussed in Chapter 21

Greater diagnostic difficulty is afforded when the organic factor is an acute coronary thrombosis or an intimal hemorrhage with extreme reduction in size or occlusion of the coronary lumen but without myocardial infarction Although viability of muscle is maintained by collateral circulation the coronary reserve is minimized or eliminated and anginal pain occurs at rest or with minimal

stress Under such circumstances the patient should be inactivated chiefly by rest in bed for about two weeks to permit the development of intercoronary anastomoses and to prevent the development of myocardial necrosis during the unstable period When collaterals are developing anticoagulants may be as desirable as if one were treating a patient with coronary occlusion and myocardial infarction Nitroglycerin should be administered as often as necessary to relieve pain or prophylactically to minimize the frequency of attacks

The appearance of angina decubitus without objective signs of myocardial infarction also suggests an acute coronary occlusion without infarction It is presumed that *coronary reserve is now minimal* but usually adequate when the patient is upright With recumbency the increased venous return and work of the heart cannot be handled by an appropriate increase in coronary blood flow as occurs normally *An element of left heart failure may be concerned in this mechanism* Treatment should consist of elevation of the head of the bed multiple pillows special beds to permit sleep with the chest and head elevated nitroglycerin before retiring and as needed to relieve pain a two-week rest period to permit stabilization of a collateral circulation anticoagulant therapy if feasible as well as a therapeutic trial of measures to control left-sided heart failure (Chap 11)

When a patient is first seen within a *few days* after his first attack of angina pectoris it is probable that an acute coronary occlusion has also occurred (p 457) even when there is no myocardial infarct and he is treated as above with modified bed rest and so on in the hope of avoiding myocardial infarction and permitting the development of a collateral circulation This does not apply to the patient who already has stabilized chronic angina pectoris when first observed

Occasionally the organic factor which suddenly reduces the coronary reserve is not a coronary occlusion but a non-cardiac disease such as anemia due to gastrointestinal bleeding or a hemolytic anemia pulmonary embolism or other condition producing shock with or without coronary constriction Under these circumstances the causative factor should be treated and corrected if possible Loss of coronary reserve and intensification of anginal symptoms in calcific aortic stenosis or syphilitic coronary ostial narrowing may represent the last stage of a progressive disease and the outlook is poor but they may also be due to a complicating coronary atherosclerotic occlusion to which the heart may adjust or to a remediable non-coronary factor

Finally the intensification of angina pectoris may not be followed after a variable period by readjustment and clinical improvement Under such circumstances the frequency and severity of attacks of pain their occurrence with minimal or no apparent provocation and the enforced limitation of activity render the patient both miserable and an invalid When these symptoms persist for at least six months despite every *effort to eliminate or alleviate any possible* contributory factor and despite the frequent use of nitroglycerin and other drugs which sometimes appear helpful the angina pectoris may then be labeled intractable The *psychic factors which are apparent in many* patients often present great difficulty in evaluation of the angina pectoris Psychotherapy should always be employed in patients with intractable angina Recently I have observed a dramatic response to what was termed intractable angina pectoris for two years following the administration of chlorpromazine (Thorazine) I have a series of patients with persistent anginal pain weakness and other symptoms following myocardial infarction who have had a good clinical response after electric shock or electronarcosis therapy However when there is no clear indication for such procedures in a patient with intractable angina pectoris I usually recommend the induction of myxedema with radioactive iodine (I^{131}) If this is not accepted or is ineffective I consent to the *performance of the Thompson (p 485) or* Beck I operation (p 486) It is important that the patient with intractable angina pectoris should not be rendered an addict to opiates while the physician is deciding to await the effect of simple medical therapy

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Chapter 19

ACUTE CORONARY OCCLUSION AND MYOCARDIAL INFARCTION

Etiology, Pathologic Physiology and Pathology

Definitions

Coronary thrombosis refers to the disease associated with an acute thrombotic occlusion of a major coronary artery The thrombosis is almost always a complication of coronary atherosclerosis and is an intrinsic stage of the atherosclerotic process Acute *coronary occlusion* is a more inclusive term denoting the sudden obstruction of a coronary artery either by the development of a thrombus or by an intimal hemorrhage with swelling of the arterial wall or by an embolus

Myocardial infarction signifies the necrosis or death of a portion of heart muscle because of an interruption or curtailment of its blood supply While it is usually the result of an acute coronary occlusion, infarction of the myocardium may also occur without mechanical obturation of a coronary artery, following a sharp reduction in the volume or oxygen content of the coronary blood due to circulatory or hematologic disturbances *Cardiac infarction* may be a more accurate designation than myocardial infarction in many instances in which the pericardium and endocardium as well as the heart muscle are affected by the coronary occlusion

Coronary thrombosis is associated with a distinctive clinical picture characterized usually by pain in the chest, similar in location and radiation to that of angina pectoris but differing in its greater severity and duration, in its usual independence of exertion and especially in its frequent association with evidences of shock and of acute left ventricular failure, fever leukocytosis and persistent and progressive electrocardiographic changes Actually these clinical features are due to myocardial infarction and not to the coronary occlusion as such Prolonged clinical usage and the usual concomitance of coronary occlusion and myocardial infarction have justified the interchangeable use of these terms when referring to the above clinical syndrome But for clarity in the interpretation of the clinical and laboratory phenomena it is essential to understand that they issue from the infarcted heart muscle and not from the coronary occlusion per se

This distinction is important, for acute coronary occlusion and myocardial infarction are not invariably associated It is now recognized that coronary occlusion may and frequently does occur without ensuing infarction,[8] and conversely that myocardial infarction may develop in the absence of an acute coronary occlusion [27] The same clinical picture is associated with myocardial infarction whether or not the latter is due to an acute coronary occlusion, on the other hand the above mentioned characteristic pain, fever leukocytosis and typical electrocardiographic changes do not follow the occlusion unless myocardial infarction ensues

Frequency and Importance of Acute Coronary Thrombosis

As heart disease is now the acknowledged greatest single cause of death in this country so coronary thrombosis is the most important cause of heart disease The cardiac mortality rate in 1940 was 292 5 per 100 000 population and 25 per cent of this was attributed to disease of the coronary arteries most of the latter undoubtedly represented coronary thrombosis and its consequences Another 46 per cent of the cardiac mortality was attributed to chronic myocarditis and myocardial degeneration, which surely includes a large

though undefined percentage of cases of acute and chronic coronary thrombosis In 1950 the crude death rate from all forms of heart disease was 354 2 per 100 000 145 4 representing that due to diseases of the coronary arteries [64]

The Increased Incidence of Coronary Thrombosis

There has been a progressive increase in the reported incidence of coronary occlusion and this rising curve of mortality has not yet levelled off The crude death rate from coronary disease had risen from 7 9 per 100 000 in 1930 to 23 1 in 1935 subsequently this increased to 71 4 in 1940 and to 226 1 in 1952 That the increase is real not merely due to improved diagnosis or more complete reports was indicated by the studies of Morris [65] In part the increased incidence is due to the reduction in childhood and other infections and to other advances in medical knowledge In consequence a larger proportion of the population reaches the age groups in which death from atherosclerotic coronary thrombosis is frequent

ETIOLOGY OF ACUTE CORONARY OCCLUSION

UNDERLYING CAUSES

Atherosclerosis of the Coronary Arteries

This is responsible for at least 95 per cent of the cases of acute coronary occlusion The etiology of atherosclerosis itself has been discussed in Chapter 16 p 417 This chapter is concerned essentially with acute coronary occlusion due to atherosclerosis Very rarely an acute occlusion is due to other causes including syphilitic occlusion of the ostia of the coronary arteries (p 894) and coronary embolism (p 440) and very rarely periarteritis nodosa dissecting aneurysm of the aorta (p 556) neoplasms or tuberculosis and possibly rheumatic fever and thromboangiitis obliterans Myocardial infarction due to granulomatous giant-cell arteritis of the type causing temporal arteritis has been reported [67] A case of myocardial infarction due to dystrophic calcification of the coronary arteries associated with calcification of the adrenal and thyroid glands was reported in an 8 week old infant [68]

CONTRIBUTORY AND PREDISPOSING FACTORS

The contributory and predisposing factors in acute coronary thrombosis and myocardial infarction are those which are concerned with the underlying coronary atherosclerosis and have been discussed (p 416) See also p 1034

Hypertension and Diabetes

Hypertension [4, 49, 29] and diabetes [33, 71, 72, 70, 1] are particularly important but not essential to the occurrence of coronary thrombosis The relative infrequency of coronary thrombosis in females in the absence of hypertension or diabetes is still worthy of note [43, 5, 4]

Familial Hypercholesterolemia (p 425)

Myxedema (pp 1017 1020)

Polycythemia (p 1051)

Disease of the Biliary Tract

A possible association of disease of the biliary tract and coronary heart disease including coronary thrombosis was discussed under angina pectoris

Age

At least 90 per cent of the cases of acute coronary thrombosis and myocardial infarction occur in persons between the ages of 40 and 70 My own experience corresponds with those studies which have revealed a somewhat higher incidence between the ages of 50 and 60 than in any other decade [61] but others have found the peak between 60 and 70 [42, 44, 45] As the ability to diagnose acute coronary thrombosis has improved and become widely disseminated this disease has been recognized with increasing frequency in subjects below the age of 50 and even before the age of 40 Furthermore it is highly probable that there has been a real increase in the incidence of coronary thrombosis with acute myocardial infarction before the age of 40 The occurrence of this condition in young persons previously reported as occasional has been emphasized by reports of large series of cases among soldiers between the ages of 18 and 40 [4, 51, 52, 53, 54, 24, 19] Most of these cases were fatal as a rule death occurred suddenly and unexpectedly Probably 5 per cent of first attacks of acute coronary thrombosis occur before the age of 40 Rarely proven cases have even been observed in childhood and infancy Thus although acute coronary thrombosis with myocardial infarction is essentially a disease of middle life and thereafter it may occur at any age and youth is no contraindication to its diagnosis when the history and findings are characteristic

Sex

There is a notable preponderance of males among patients suffering from acute coronary thrombosis Reported series of cases indicate a

ratio of males to females varying between 2 to 1 and 6 to 1[4, 49, 4, 51, 52] The ratio of 3 to 1, based on studies of cases at autopsy, is probably more accurate than the higher ratios reported in clinical series The preponderance of males is most striking in those cases of coronary occlusion in which there is neither hypertension nor diabetes mellitus Several explanations have been offered for the lesser susceptibility of women to coronary atherosclerosis and thrombosis,[38] notably the difference in lipid metabolism and the effect of estrogens (Chap 16)

On the other hand there was a recent report of an unexpectedly high incidence of myocardial infarction in the Negro female[3,9] In addition myocardial infarction was found to be associated much less frequently with angina pectoris and was associated with a higher fatality rate than that in the white race and in the Negro male

Occupation

There are insufficient data to permit a definite conclusion as to the etiologic relationship between occupation and the occurrence of coronary thrombosis[48, 57] It is improbable that occupation is an important predisposing factor The statistical and epidemiologic surveys of Morris et al[58] indicated that men in physically active jobs have a lower incidence of coronary heart disease and less severe disease than men whose work requires less physical activity

Heredity

Hereditary susceptibility appears to be a more fundamental etiologic factor in the occurrence of coronary atherosclerosis and occlusion than most of those already mentioned Every physician who has obtained a careful and accurate family history in his patients with coronary artery disease must have been impressed by the frequency with which angina pectoris, sudden death or proven attacks of acute coronary thrombosis occur in several members of the same family I have found this family tendency to be most striking in patients who suffered their acute coronary occlusion at an early age One of my patients died of his first coronary occlusion at the age of 35 and his only brother of the same cause at 39 Their father had died suddenly at 40 and their paternal grandfather had also died suddenly in his early forties, both presumably of a heart attack Hypertension cerebral hemorrhage or thrombosis and diabetes mellitus appear to occur with more than average frequency in the same families[4] The hereditary factor in familial hypercholesterolemia and xanthomatosis and its relation to coronary occlusion has been noted (p 425)

Body Build (p 416)

Temperament

The rising incidence of acute coronary thrombosis has sometimes been attributed to the increased strain of modern living Many patients with this disease disclose a history of recent or prolonged psychic conflict and emotional stress For this reason, coronary thrombosis, like hypertension, peptic ulcer and hyperthyroidism has been interpreted by some as primarily a psychosomatic disease occurring in specific susceptible personality types[1] Many of the patients with advanced coronary disease may be described as aggressive ambitious individuals with an intense physical and emotional drive, who have no hobbies and have not learned to play, and who have concentrated all their thoughts and energy in the narrow groove of their career However it need hardly be mentioned that there are also patients with coronary occlusion who do not fit this description The interpretation of this condition as primarily a psychosomatic disease has little scientific support at the present time However, the possible importance of psychic factors in the etiology of coronary artery disease is worthy of careful investigation

Tobacco (pp 416 451)

PRECIPITATING FACTORS

We have seen that attacks of angina pectoris occur promptly after certain precipitating factors such as effort, exposure to cold the intake of food and emotional excitement Although an acute coronary occlusion also appears to develop suddenly, its precipitating factors are still unknown and the causes responsible for attacks of angina pectoris do not usually initiate a coronary occlusion Analyses of the events immediately preceding episodes of acute coronary occlusion have not usually demonstrated a causal relationship between specific activities and the occlusion

Physical Exertion

In a study of patients' activities immediately prior to an acute coronary occlusion in 437 cases, Phipps[63] noted physical exercise in only 13 per cent and moderate or usual exertion in 18 per cent while in 51 per cent of

the cases the patient was at rest and in 8 per cent asleep Surgical procedures had been performed in 6 per cent In 19 per cent of the cases the occlusion had occurred during moderate exertion after a heavy meal and in 12 per cent after a meal but with the patient at rest Similar investigations by Master Dack and Jaffe[43] revealed that among 1108 attacks of acute coronary thrombosis 52 per cent occurred while the patient was asleep or resting 21 per cent during mild routine activity 16 per cent while the patient was walking and 9 per cent during moderate activity In only 2 per cent was there a history of unusual physical exertion This analysis led the authors to conclude that the percentage of attacks which occurred during sleep rest or mild moderate or intense activity coincided with the proportion of the day spent in these states and that physical exertion which is an important precipitating factor of angina pectoris is not concerned in the initiation of acute coronary occlusion

Unfortunately such studies may be invalidated by the difficulty of obtaining an accurate and complete history and especially by the nature of the pathology of coronary occlusion Although the characteristic symptoms of acute coronary occlusion usually develop suddenly the underlying pathologic process and functional disturbances associated with the occlusion may commence hours or days before distinctive symptoms appear Sometimes there are premonitory symptoms during this period which are forgotten by the patient in the throes of the more intense symptoms of the full blown attack Not infrequently the patient denies any unusual effort prior to the occlusion but questioning of a relative friend or business associate discloses some extraordinary or dramatic activity which might have been causal Since the actual occlusion precedes the striking symptoms of the attack by hours or days the factors responsible for the occlusion may have acted hours days or even weeks before the appearance of symptoms Therefore efforts to discover the precipitating cause by recording the events or activities immediately preceding the first major symptom of an acute coronary occlusion may be misleading

While the observations of Phipps[52] and of Master et al [43] indicate that physical exertion is not a precipitating cause of acute coronary occlusion other authors have reported cases in which there is strong circumstantial evidence for such a causal relationship Among 100 cases of acute coronary occlusion Fitzhugh and Hamilton[24] noted that the occlusion had occurred 24 times during or promptly following some unusual and violent physical exertion and 33 times after an unusual exertion which was not necessarily violent Boas[10] reviewed reported cases of cardiac infarction following unusual effort and described briefly 13 out of 25 cases which had come under his personal observation Cooksey[14] found that 17 out of 100 private cases of acute coronary occlusion had developed within 24 hours of definitely unusual and frequently extreme physical exertions Smith and associates[73] found that physical exertion was associated with the attack in 32 of 53 cases of coronary occlusion Yater and associates[9] reported that the proportion of attacks among young soldiers occurring during strenuous activity was more than twice as great as the proportion of time spent in such activity French and Dock[26] found that 26 or 3› per cent of 80 fatal attacks of coronary disease occurred within one to several hours after vigorous exercise The exertions reported as unusual or severe by the various authors included cranking a car in cold weather lifting a heavy trunk pushing a stalled auto rowing long hikes uphill etc all of which had never been performed previously by the patient in question or had not been done for many years Fitzhugh and Hamilton[24] emphasized that the effort had often been performed when the subject was suffering from undue fatigue inadequate sleep and excessive emotional strain In conclusion while the evidence adduced by Master and his associates[43] might indicate that physical exertion is not an essential or even important precipitating cause in most cases of acute coronary thrombosis it does not exclude the possibility that it induces at least some of the instances of coronary thrombosis

Several suggestions have been offered to explain a possible causal relationship between physical exertion and acute coronary occlusion and myocardial infarction The mechanism which often initiates the actual occlusion is probably a capillary hemorrhage within an atherosclerotic plaque in the intima [5, 50] ■ Paterson[5] suggested that a ■ e in arterial blood pressure associated with physical exertion and emotion may be responsible for the

rupture of intimal capillaries and a subsequent thrombosis Physical exertion may also be indirectly related to the development of a myocardial infarct after an acute coronary occlusion has already occurred Because of a collateral circulation the occlusion itself may not produce sufficient myocardial anoxia to result in infarction Severe physical effort at this time by augmenting the work of the heart, may enhance the degree of anoxia and cause necrosis of myocardial tissue This suggestion is supported by the finding of Yater and associates[3] that only 11 per cent of those patients with coronary artery thrombosis who died in bed had old or organizing thrombi while 38 per cent of those engaged in strenuous activity had such thrombi Similarly the observation of French and Dock[26] that a fatal attack during exertion was often associated with severe coronary artery narrowing but no occlusion may indicate that the exertion intensified a potential or relative coronary insufficiency to the point of causing fatal myocardial anoxia

Emotional Strain

Emotional strain even more than physical exertion is difficult to evaluate as a factor in the occurrence of an acute coronary occlusion The purported increase in the incidence of this condition has been loosely attributed to the stress of modern living Clinical histories upon which such conclusions are based are usually incomplete or unreliable for they are deficient in the necessary psychiatric detail They often fail to include possible causative emotional disturbances which have occurred days or even weeks before the attack The duration as well as the intensity of the emotional disturbance may be of etiologic importance Emotional strains are varied in character and must be interpreted in terms of their effect on the individual and his reaction to them In eliciting a history of emotional disturbance one must be certain that a similar history could not be obtained from numerous persons without a coronary occlusion or even from the patient himself during many previous years when he was perfectly well But despite these difficulties and uncertainties I do not wish to dismiss the possible relation of emotion to the precipitation of acute coronary occlusion without comment I have so often noted the occurrence of this condition in persons who had been under an unusually severe and protracted emotional strain that I believe this possible relationship is worthy of serious study Its implications in prophylaxis and therapy are obvious

Coronary thrombosis has been observed after an acute emotional experience as well as after prolonged emotional stress Boas[11] has reported some historical as well as personal cases of this type

Trauma[39, 43]

Trauma may produce a pericardial and myocardial contusion with hemorrhage into and destruction of the muscle tissue of the heart (Chapter 44) The resulting clinical picture may resemble that of myocardial infarction Or the injury may involve a large coronary artery and induce a coronary thrombosis with true myocardial infarction[41] The injury may be of the penetrating variety, such as a stab or gunshot wound, but similar consequences may result from nonpenetrating blows to the chest wall (p 1063)

These cases of traumatic myocardial contusion or of direct injury and thrombosis of a coronary artery must be distinguished from cases of atherosclerotic coronary occlusion in which unusual physical exertion appears to be a possible precipitating factor In the former, the essential causative role of the trauma may be supported by the finding at necropsy of a myocardial hemorrhage or an injured and thrombosed artery in a heart whose vessels are otherwise relatively normal In the latter cases the occlusion is found in a markedly atherosclerotic vessel

Operations

Attacks of acute myocardial infarction soon after operation have been observed with sufficient frequency to suggest that there is a significant causal relationship between the operation and the acute infarction[8] In most instances of acute myocardial infarction postoperatively the infarction is secondary to an acute coronary occlusion on an atherosclerotic basis In other cases however the infarction occurs without associated coronary occlusion The occurrence of shock with its associated fall in blood pressure could reduce the coronary blood flow and result in sufficiently severe myocardial anoxia to cause necrosis of muscle even though the coronary vessels were not occluded (p 505) This mechanism could be intensified by hemorrhage, dehydration and tachycardia The possibility of a coronary occlusion after an operation often poses a problem in the diagnosis of

postoperative complications since the classic pain associated with myocardial infarction may be absent or overshadowed by other symptoms in these cases and since postoperative myocardial infarction may closely resemble surgical shock and pulmonary embolism.

Among other factors[11] which have been reported as occasional precipitating or contributing causes of acute myocardial infarction are infections of the respiratory tract, insulin hypoglycemia,[29] artificial hyperpyrexia, high altitude, drinking of ice water, injections of antitoxin,[80] serum sickness[72] and so called vascular allergy.

A history of angina pectoris has been noted in one third to two thirds of cases of acute myocardial infarction. This merely denotes that clinical evidence of advanced coronary atherosclerosis or previous coronary occlusion often precedes a fresh coronary thrombus and cardiac infarct.

PATHOLOGIC PHYSIOLOGY

THE EFFECT OF EXPERIMENTAL ACUTE CORONARY ARTERY LIGATION

Mortality and Occurrence of Infarction

The early experimental attempts at acute ligation of a large coronary artery in animals usually resulted in rapid arrest of the heart and led to the conclusion that the coronary arteries were end arteries.[17] Porter[64] observed that the frequency of cardiac arrest following experimental acute coronary occlusion in dogs was dependent in part on the type of anesthetic used. More recent observers have demonstrated that acute coronary occlusion in animals is *not* invariably fatal and is compatible with long periods of survival and well being.[73]

However, if one of the three major coronary arteries is completely ligated close to its origin, a large infarct of the corresponding area of myocardium almost invariably develops.[74, 30] This corresponds in general with the usual consequence of a similar acute coronary occlusion in humans and suggests that functionally at least these vessels may act as end arteries, even though anatomic anastomoses are present and establish a *functioning* collateral circulation. On the other hand, the acute experimental occlusion of a secondary branch or the acute occlusion of a major branch in its distal portion usually causes no infarct and no significant circulatory disturbance because under such circumstances the collateral circulation is capable of maintaining an adequate blood supply to the affected area of myocardium.

Blumgart and his associates[7a] found that no structural damage to the heart muscle occurred following acute coronary artery ligation if the normal blood supply was reestablished after 5 to 20 minutes by removal of the occluding ligature; occlusion for more than 20 minutes produced focal areas of necrosis and fibrosis or massive infarction. These observations suggest that extreme myocardial anoxia results in irreversible muscular disturbance and necrosis only if prolonged beyond a minimum interval. Similarly, in human cases of cardiac pain which represent myocardial anoxia, persistence of pain for 20 minutes or more probably denotes that anatomic damage has occurred. Blumgart and associates[8] also noted that survival usually occurs if a major coronary artery is narrowed to not less than 15 to 19 per cent of its original cross section. Following such extreme narrowing it required at least 12 days for a rich collateral anastomosis, more than 40 micra in diameter, to develop.

Mechanical, Thermic, Chemical and Electrocardiographic Changes

Following experimental acute coronary artery ligation a variety of disturbances occur including (1) prompt cyanosis and weakness or loss of contraction of the muscle which loses its blood supply;[66] (2) a fall in local temperature[4] and an increase in lactic acid and muscle glycogen;[36] (3) serial changes in T waves, S-T segments and initial deflection,[73, 83] or the so-called ischemia injury pattern[2] characterized by a primary T wave inversion (ischemia) followed by R-T elevation (injury); (4) disturbances in rhythm including ectopic beats and frequently ventricular tachycardia followed by fatal ventricular fibrillation; (5) a diminished stroke output and a delay in circulation time.[3] These abnormalities can usually be reversed if the clamp occluding the coronary artery is released in 20 minutes.

Anatomic Changes

In contrast with the prompt electrical, thermal and chemical changes following experimental acute coronary artery occlusion, no histologic changes were observed by Tennant et al.[87] until 8 hours after the liga

tion After this interval, edema of the interstitial tissue and the deposition of fat droplets were noted, after 28 hours necrosis and increased fatty deposits in the muscle fibers, and an infiltration of polymorphonuclear leukocytes and red blood cells in the interstitial tissue were observed, after 48 hours fibroblasts appeared Healing became prominent after four days, and after four weeks the infarcted zone was replaced by a dense fibrous tissue scar These alterations developed only if the ligature was maintained for 2 to 8 hours, if the ligature was released after an interval of 30 minutes or less there were no demonstrable histologic changes Viability and healing of tissue are dependent on immediate retrograde flow into the ligated coronary artery from other coronary arteries and a more gradual development of an extensive interarterial collateral circulation after two to four weeks[9, 33]

Histochemical studies of myocardial tissue indicate that there is a reduction in enzyme activity such as that of succinic dehydrogenase in the early hours after experimental coronary occlusion even before any changes are demonstrable by routine staining techniques [illegible]

Mallory, White and Salcedo-Salgar[48] noted that the conversion of a small infarct into a scar occurred in two weeks while large infarcts required five weeks for this healing process Cardiac rupture occurred occasionally usually in the second week after the experimental occlusion These observations correspond in a general way with the pathologic changes in human coronary occlusion and form an experimental support for the clinical practice of keeping patients in bed for at least three weeks and preferably six weeks after the occurrence of an acute coronary occlusion

EXPERIMENTAL CHRONIC CORONARY ARTERY LIGATION

Although experimental acute coronary occlusion is followed by changes which resemble those in human cases human acute coronary occlusion differs in that it is usually preceded by a more or less prolonged period of progressive coronary narrowing during which there is an opportunity for the development of a collateral circulation Therefore, in order to simulate more closely conditions in the human disease attempts have been made to produce a gradual coronary occlusion in animals

Beck and Tichy[5] effected a gradual obturation of a large coronary artery by repeated pinching with metal clips Robertson[69] occluded the major coronary arteries in succession by serial ligation during a period of months Blum, Schauer and Calef[7] gradually narrowed a major coronary artery near its origin by progressive tightening of a modified Goldblatt clamp for a period of five weeks until there was complete occlusion The latter experimenters noted that in a control series of 25 dogs which had survived an acute coronary occlusion, a large infarct developed in 24 animals and a small infarct in the remaining one On the other hand extensive myocardial necrosis was observed in only 4 out of 14 dogs in which they had occluded the same coronary artery gradually They concluded that the collateral circulation developing during gradual coronary artery occlusion sufficed to prevent a large part of the myocardial damage which resulted when the same vessel was occluded suddenly In similar experiments Burchell[14] produced chronic coronary occlusion in the three main coronary arteries by first constricting them with metal clips for three weeks to three months and then ligating the vessels He also noted that the complete closure of a large coronary artery did not necessarily result in myocardial infarction if the occlusion was produced gradually

These experimental observations correspond to the findings in cases of human coronary occlusion in which myocardial infarction is a frequent but not an invariable consequence They indicate that with gradual coronary narrowing anastomotic vessels may provide a collateral circulation sufficient to prevent infarction even when the actual occlusion is complete and sudden On the other hand the frequency with which infarcts appear even after gradual coronary occlusion attests to the imperfection of the collateral circulation in most instances

FACTORS DETERMINING THE OCCURRENCE OF INFARCTS AFTER ACUTE CORONARY OCCLUSION

A number of factors determine whether or not a myocardial infarct will result from an acute coronary occlusion which occurs after a period of gradual narrowing as in human cases of this condition

1 **The Size of the Occluded Artery** Occlusion of any one of the major coronary arteries the left anterior descending the left circumflex or the right coronary is usually followed by a myocardial infarct occlusion of any of the smaller branches rarely causes significant myocardial necrosis

2 **The Site of Occlusion** The probability of myocardial infarction increases the nearer the site of occlusion is to the origin of a major coronary artery The more distal the occlusion the more vessels are available proximal to the occlusion to provide a collateral circulation

3 **The Speed of Occlusion.** Sudden complete occlusion in a normal large coronary artery is almost always followed by an infarct because an adequate collateral circulation has not been established However coronary embolism usually causes a prompt fatality before an infarct can develop With progressive narrowing prior to occlusion as in coronary atherosclerosis the changes in pressure gradients in anastomotic vessels permit a gradual progressive increase in the relative blood flow through these collateral channels When complete obstruction occurs the myocardium affected may be receiving its major blood supply from these enlarged collateral vessels and the occlusion of the original supplying vessel may not be of serious consequence

4 **The Condition of the Other Major Coronary Arteries** Myocardial infarction is less likely to follow an acute coronary occlusion if the other two major vessels are normal than if one or both are already occluded or extremely narrowed Under the latter circumstances the possibility that the remaining vessels will provide an adequate collateral circulation is less than if they were normal In fact the first coronary artery occlusion often causes no infarction because an adjacent major artery provides sufficient blood to the affected area This occlusion may however result in relative myocardial anoxia when the work of the heart is increased and may be manifested clinically by angina pectoris on effort However if the second major artery which provided the collateral circulation is then occluded a myocardial infarct usually results because the first major artery supplying the area of myocardium is already closed

5 **The Anatomic Pattern of the Coronary Arteries** The distribution of the coronary arteries varies in different hearts particularly with regard to the proportion of cardiac muscle supplied by the left or right coronary arteries respectively Schlesinger[75] observed myocardial infarcts with the least frequency in the hearts with a balanced coronary circulation next in those with a right coronary artery predominance and most frequently in those hearts in which there was a preponderant blood supply from the left coronary artery Furthermore in the left coronary preponderant group the first infarct was most likely to be fatal whereas multiple infarcts (fresh and healed) were most common in the right preponderant group

6 **The Effect of Cardiac Hypertrophy and Other Factors.** The deleterious effect of an acute coronary occlusion on the corresponding myocardial area may be intensified by associated diseases of the heart and circulation If the heart is hypertrophied because of hypertension rheumatic cardiovalvular disease or syphilitic aortic insufficiency there is a potential myocardial anoxia because of the increased need for blood due to the greater muscle mass and the augmented cardiac work The slightly increased blood flow in hypertrophied hearts is relatively much less than the increased requirement The acute obstruction of a major coronary artery is therefore more apt to produce myocardial infarction than in a normal sized heart In the presence of anemia the probability of myocardial infarction following acute coronary occlusion may be similarly enhanced

PATHOLOGY OF ATHEROSCLEROTIC CORONARY ARTERY OCCLUSION AND CARDIAC INFARCTION

MECHANISM OF ATHEROSCLEROTIC CORONARY OCCLUSION

The pathology of coronary atherosclerosis has been described (p 429) Briefly the process consists of thickening of the intima by cellular hyperplasia and fibrosis associated with the deposition of lipids Newly formed capillaries appear in the thickened intimal plaque Degenerative changes result in hyalinization and areas of softening (atheroma or atheromatous abscess) containing a gruel like detritus of cells and lipoid material Calcification of the atherosclerotic intimal plaque occurs commonly and occasionally spicules of bone are formed The atheromatous abscess may break into the lumen forming the atheromatous ulcer the surface of which may

be covered by thrombus The artery becomes irregularly thickened and may be transformed into a more or less rigid tube The thickening occurs at the expense of the arterial lumen which may become extremely stenosed

It was formerly believed that occlusion of an atherosclerotic coronary artery was due almost exclusively to obturation of the lumen by a thrombus deposited on an athero sclerotic plaque or atheromatous ulcer But it has been demonstrated that atherosclerotic coronary occlusion may occur without thrombosis and that capillary hemor rhages into the atherosclerotic intima are frequently important in the production of occlusion with or without thrombosis[6, 90, 94] In a study of 100 autopsied cases of acute athero sclerotic coronary artery occlusion Horn and Finkelstein[37] observed that the closure was due to intramural hemorrhage in 62 5 per cent and to formation of a thrombus on an atherosclerotic plaque in 37 5 per cent of the cases

One or more of the following mechanisms are now believed to be concerned in the occlusion of an atherosclerotic coronary artery

1 **Intimal Hemorrhage with Rupture into the Lumen and Secondary Thrombosis** Owing to the degenerative necrotic changes in the atherosclerotic intima the perivascular tissue no longer provides adequate support against the intracapillary pressure Consequently the intimal capillaries often rupture and produce an intramural hemorrhage According to Paterson[6] changes in coronary arterial blood pressure (e g due to hypertension, physical and emotional stresses) may predispose to or precipitate intimal hemorrhage Such hemor rhages may occur frequently, as part of the atherosclerotic process without necessarily leading to coronary occlusion When there is extensive intimal degeneration associated with atheromatous abscess, even a small intimal capillary hemorrhage may rupture the arterial endothelium A thrombus forms at the site of the endothelial tear and leads to occlusion of the arterial lumen Occasion ally the capillary hemorrhage does not itself rupture the arterial endothelium, but may by exaggerating the already extensive intimal degeneration initiate subendothelial and endo thelial necrosis and consequent thrombosis

2 **Intimal Hemorrhage with Occlusion by Intramural Hematoma** Sometimes the athero sclerotic process causes such thickening of the arterial wall that only a very small lumen remains Rupture of an intimal capillary may result in an intramural hematoma The swell ing thus induced may be sufficient to occlude completely the already narrowed arterial lumen, even without the occurrence of thrombosis[96]

3 **Coronary Thrombosis on an Atherosclerotic Intimal Plaque** In most cases of atherosclerotic coronary thrombosis, the occlusion is not precipitated by intimal capillary hemor rhages The intima may disclose merely dense fibrous thickening and lipoid infiltration or extensive necrosis and atheromatous ulcer It is probable that the thrombosis is precipitated by arterial endothelial damage by direct im pingement of the atheromatous abscess or by rupture of the abscess into the lumen or by other subendothelial degenerative changes Leary[40] has emphasized the occurrence of coronary artery thrombosis at the site of atheromatous ulcers, and Saphir and his associates[74] noted that in their 32 cases of cor onary thrombosis the thrombi were located on atheromatous ulcers In general the throm bosis occurs in the region of the most extensive arteriosclerotic change and at the point of greatest narrowing

PATHOLOGY OF CORONARY THROMBI

Multiple coronary thrombi are found more often than a single thrombus Many thrombi are overlooked because of failure to examine carefully all of the important branches of the coronary arteries throughout their entire extent Occasionally a thrombus is expelled by the dissecting scissors By making serial cross sections of the various coronary arteries with the scalpel at intervals of 3 to 5 mm Gross and I[31] observed multiple fresh and old coronary occlusions in about 85 per cent and a single coronary occlusion in only 15 per cent of 120 hearts with coronary occlusion Saphir and his associates[74] noted more than one oc clusion or extreme narrowing in every one of 34 hearts which they examined Blumgart Schlesinger and Davis,[8] in a study of hearts by a combined injection and dissection method, also found that more than one oc clusion was usually present in the hearts showing advanced coronary atherosclerosis, thrombosis or myocardial infarction

Fresh and old coronary occlusions are usually found in the same heart Fresh thrombi appear red and are soft and friable

They are loosely adherent to the arterial wall and easily dislodged The thrombi undergo organization early After 24 hours fibroblasts and capillaries appear[6] Within a few days the red blood cells degenerate and are gradually absorbed and the fibrin is re placed by collagen The thrombus during this period appears brownish and is more firmly attached Eventually it undergoes complete fibrous replacement and the pigment dis appears The thrombus becomes firm and gray and is securely attached to the wall of the artery Recanalization of the lumen occurs commonly and may lead to a partial but in adequate reestablishment of the circulation Frequently it is impossible to determine with certainty whether we are dealing with an old recanalized thrombotic occlusion or with ex treme atherosclerotic narrowing or oblitera tion of the lumen for vascular channel forma tion in an atherosclerotic plaque may closely simulate recanalization of an old healed thrombus

LOCALIZATION OF CORONARY ARTERY OCCLUSIONS

It was formerly believed that occlusion occurred predominantly in the anterior de scending branch of the left coronary artery Levine and Brown[4] noted occlusion of the left anterior descending branch 39 times and of the right coronary artery only twice in their 46 cases of fatal coronary thrombosis More recent studies have disclosed that coronary occlusion occurs with almost equal frequency in the left anterior descending and the right coronary arteries while occlusion of the left circumflex coronary artery develops somewhat less often In addition occlusions are found not infrequently in somewhat smaller branches such as the ramus primus of the left anterior descending and in the branch to the obtuse margin of the heart which arises from the left circumflex In 100 autopsied cases of acute coronary artery occlusion Horn and Finkelstein[17] observed 61 occlusions of the right coronary artery (right circumflex) 56 in the left anterior descending 27 in the left circumflex 15 in the ramus primus and 7 in the branch to the obtuse margin

In my experience occlusions are found most commonly in the proximal portions of the affected vessels but rarely in the first two centimeters The former belief that the region from 2 to 3 cm from the origin of the left anterior descending artery was a site of special predilection for coronary thrombosis has not been substantiated by more recent careful studies Blumgart and his associates[3] described a great variety of localization of the occlusions within each of the major arteries The relative freedom from occlusion of the proximal 2 cm of the vessels is of particular importance because it permits a free circula tion through the first branch or two proximal to the occlusion by means of which a col lateral circulation may be maintained This explains the possibility of survival of humans and experimental animals even after multiple occlusions involving both coronary arteries

OCCURRENCE AND LOCATION OF CARDIAC INFARCTION

The occlusion of one major coronary artery may not be followed by cardiac infarction either because death ensues too rapidly i e within a period of minutes or a few hours or because the flow of blood through collateral channels maintains the viability of the af fected myocardium The former circumstance is noted chiefly in cases studied by coroners Thus Benson[6] observed 54 instances of recent coronary thrombosis without infarction among 1750 autopsies in the Portland morgue Usually myocardial infarction follows the recent occlusion of two major coronary ar teries or it results from one recent occlusion in the presence of at least one old occlusion or the extreme narrowing of one or more large branches However myocardial infarction may follow the first acute coronary thrombo sis provided death does not result within the first few hours thereafter

In most cases the infarct lies within the area of myocardium supplied by the recently oc cluded vessel The extent of the infarct varies considerably from laminar patches 1 to 2 cm in diameter to widespread areas of necrosis which extend through and through from the endocardium to the pericardium *Occlusion of the left anterior descending artery* often causes infarction of the anterior wall of the left ventricle near the apex but more extensive areas of the anterior wall of the left ventricle of the papillary muscles and of the anterior portion of the septum may be involved *Occlu sion of the left circumflex artery* usually pro duces infarction of some portion of the lateral wall of the left ventricle or of the posterior wall near the base *Occlusion of the right circumflex*

artery usually results in an infarct of the posterior wall of the left ventricle near the base, and it may include a variable portion of the posterior half of the interventricular septum. The septum has such a rich anastomotic circulation that it is rarely infarcted to any great extent unless both major vessels are occluded or unless one is severely narrowed and the other occluded. Infarction of the region of the atrioventricular node usually is due to occlusion of the right coronary artery close to its origin.

The location and extent of the infarct depend not only on the size and location of the vessel recently occluded but also on the presence or absence of other occlusions, recent or old, on the degree of narrowing of unoccluded vessels, on the volume of the collateral circulation in adjacent vessels, on the anatomic pattern of the coronary vessels, as well as on other factors. These variables account for the frequent lack of correspondence between the site of infarction and the area normally supplied by the occluded artery. Thus an initial occlusion of the obtuse marginal branch of the left circumflex artery may produce *no infarct* of the posterolateral wall of the left ventricle which it supplies, because this region may continue to receive an adequate blood supply from collateral branches of the right circumflex. A subsequent acute occlusion of the right circumflex, by eliminating this collateral circulation, may produce infarction of the area formerly supplied by the now occluded left circumflex branch, whereas the posterior wall of the left ventricle supplied by the right circumflex maintains its viability through collaterals from the main left circumflex. A collateral circulation is frequently provided by branches of the occluded artery, arising proximal to the occlusion.

In a detailed study of both the coronary arteries and the myocardium in 25 hearts from patients with clinical coronary heart disease, Snow et al.[8] observed that almost all coronary occlusions gave rise to myocardial infarcts, even when the occlusion occurred in a previously narrowed vessel. This finding did not support the concept that gradual narrowing of a coronary artery leads to the development of collateral vessels which are capable of preventing infarction when the vessel is occluded. Furthermore, these observers discovered that not only did major occlusions almost invariably cause infarction, but in addition a single occlusion frequently resulted in more than one infarct. They found that for a period of three to eight weeks after acute myocardial infarction, a period which corresponded with the time required for collateral vascularization of the ischemic area, there was frequently an extension of the initial infarct into adjacent ischemic zones.

Cardiac infarction is confined almost exclusively to some portion of the left ventricle or the interventricular septum. The right ventricle is involved rarely; Saphir and his associates[74] observed one instance of right ventricular infarction in their 34 cases of myocardial infarction, and Wartman and Hellerstein[93] 4 in 160 cases. Whether this is due to a richer coronary anastomosis,[66] to the relatively smaller myocardial mass of the right ventricle or to other factors is unknown. Occasionally infarction of the atria results from atherosclerotic coronary artery occlusion simultaneously with ventricular infarction.[7] Atrial infarcts, usually involving the right atrial appendage, were reported in 17 per cent of cases of ventricular infarction.[45] I have also seen atrial infarction in a case of periarteritis nodosa with coronary thrombosis. Within the wall of the left ventricle the site most frequently and most severely affected is the subendocardium. The papillary muscles are also frequently involved. The intermuscular branches of the coronary arteries extend perpendicularly from the main superficial vessels in the epicardium and terminate in the subendocardium. The latter represents the periphery of the coronary circulation and therefore suffers most intensely from a reduction in the coronary blood flow. The endocardium itself is adequately nourished by the blood within the cardiac lumen. In cases of patchy necrosis or infarction due to coronary insufficiency without coronary occlusion, the lesions are confined to the subendocardium and papillary muscles.

The localization of myocardial infarction according to muscle bundles has been described by Robb and Robb.[65]

MACROSCOPIC AND MICROSCOPIC PATHOLOGY OF CARDIAC INFARCTS

The earliest changes of infarction of the myocardium are those of ischemic or coagulation necrosis. The affected heart muscle appears pale, yellowish or gray. Its consistency becomes firmer and drier than that of the surrounding muscle. The periphery of the infarct

is often delineated by a more or less regular reddish zone of hyperemia. *Microscopically* at this early stage the muscle fibers are seen to have lost their nuclear structure while the nuclei of the connective tissue and blood vessels are still apparent. But soon, especially in large infarcts, the cells of the connective tissue and blood vessel walls also undergo necrosis. At an early stage the muscle cells show evidences of hyaline and granular degeneration and loss of myostriation. These changes are associated with an uneven staining of the muscle fibers resulting in the appearance of deeper and lighter eosinophilic bands.

Somewhat later there is complete necrosis of the cells of the connective tissue and blood vessels as well as of the muscle fibers. The muscle fibers become completely vacuolized and eventually there is complete homogenization or disappearance of many muscle fibers. Hyperemia of the surrounding vessels and the accumulation of *polymorphonuclear leukocytes*, lymphocytes and mesenchymal cells are evidences of reaction to the necrotic cardiac muscle. The polymorphonuclear leukocytes may invade the necrotic muscle and produce an appearance somewhat similar to that of an acute suppurative inflammation. Between the central zone of necrosis and the peripheral zone of hyperemia there may be a yellowish band of fatty infiltration due to partial anoxia. Often there is an extravasation of red blood cells from the congested vessels and the entire area of infarction may appear hemorrhagic. The infarct appears yellowish green or gray, often mottled or streaked with hemorrhage depending on the predominance of one or the other of these changes.

The infarcted muscle undergoes various degrees of friability or softening (*myomalacia*) due to the transudation of fluid from the neighboring vessels into the degenerated muscle tissue. If the degree of softening is extreme, the infarcted muscle may become the site of a small irregular tear resulting in *cardiac rupture* (p. 542). Complete rupture, usually in the anterior wall near the apex or the posterior wall at the base of the left ventricle, is followed by hemorrhage into the pericardiac sac (*hemopericardium*) and a fatal issue. Occasionally extreme softening of an infarct produces a *rupture of the interventricular septum* which may be diagnosed intra vitam and which is usually but not always fatal (p. 543). Rupture of a papillary muscle is also a rare complication of myocardial infarction (p. 543). Cardiac rupture may be incomplete and the seepage of blood through the tear produces a dissecting aneurysm of the heart which may appear as an hemispherical bulge of the cardiac surface. A considerable interval may elapse between the development of an incomplete cardiac tear and dissecting aneurysm and the occurrence of a complete rupture.

Organization of a myocardial infarct begins within a week. The necrotic material is resorbed and the infarcted area is invaded by a granulation tissue rich in blood vessels and fibroblasts. Remnants of necrotic muscle are still visible within the granulation tissue. Pigment granules giving a positive iron reaction are seen within and outside macrophages and are residua of old hemorrhage. At this stage of early organization the hemorrhagic infarct is converted into a grayish red area of healing. Eventually the granulation tissue is replaced by a dense collagenous tissue rich in elastic fibers which is converted into an avascular scar. Grossly this appears as a pearly white tendon like cicatrix of varying extent. Occasionally the healed infarct becomes more or less calcified[76] and rarely bone may be formed.[14] Fresh and old infarcts are often observed in the same heart.

Cardiac aneurysms are not infrequently associated with both fresh and old infarcts (p. 543). An aneurysm at the site of a fresh myocardial infarct is often overlooked unless the affected ventricle is distended with fluid under pressure. Where an infarct heals, the damaged myocardium may become thinned and stretched into an aneurysm. At postmortem examination the aneurysm may appear as a pale depressed area or as a localized bulge. The aneurysm may become calcified.[12]

ENDOCARDIAL AND PERICARDIAL LESIONS IN CARDIAC INFARCTS

Cardiac infarcts frequently damage or rupture the endocardial endothelium either by direct involvement of the entire endocardial thickness or by an hemorrhagic extravasation which produces a dissecting aneurysm extending to the cardiac lumen. An endocardial thrombus very often overlies fresh or healed infarcts. Mural thrombi were found at autopsy in 44 per cent of 924 cases of acute myocardial infarction reported by various observers.[24] These mural thrombi are almost al

ways situated in the left ventricle, especially at the apex. But when there is extensive infarction of the interventricular septum, mural thrombi may develop on both sides of the septum. Occasionally large semispherical masses of thrombi fill the cavity of a bulging aneurysm at the apex of the left ventricle. Although these thrombi are quite adherent to the endocardial surface superficial portions may become detached and cause embolization of the brain, the viscera or the extremities.[73] However, pulmonary emboli, which commonly complicate acute coronary occlusion, arise usually from thrombi in the veins of the lower extremities and only occasionally from mural thrombi in the right ventricle.

Cardiac infarcts extend frequently also to the pericardial surface and produce a localized or occasionally an extensive fibrinous pericarditis.[84] With recent infarcts there is a dull fibrinous exudate overlying the area of necrosis; healed infarcts are covered with a gray or white adherent patch of scar tissue. Pericarditis was observed at autopsy in 28 per cent of 111 cases of myocardial infarction analyzed by Wartman and Hellerstein.[91] Effusions develop occasionally when a wide area of pericardium is involved.[77, 89]

SIZE OF THE HEART AFTER CARDIAC INFARCTION

Cardiac enlargement or hypertrophy occurs in at least two thirds of the cases of cardiac infarction due to coronary artery occlusion. Palmer[60] observed cardiac enlargement, as determined roentgenologically, in 128 (64 per cent) of 200 clinical cases of coronary thrombosis, and Bartels and Smith[2] noted cardiac hypertrophy in 37 (88 per cent) of 42 infarcted hearts examined postmortem.

However, it is uncertain whether or how frequently cardiac hypertrophy is the direct consequence of the cardiac infarct or whether it is always due to associated conditions or to complications of the infarct. Hypertension is present in the majority of patients with coronary artery occlusion and may represent the commonest cause of cardiac hypertrophy in such cases. The etiologic role of hypertension may be overlooked because the blood pressure often falls to within the normal range after an attack of coronary artery occlusion. In other cases an associated rheumatic cardiovalvular disease or syphilitic aortic insufficiency may account for the enlargement of the heart.

But cardiac hypertrophy undoubtedly occurs in cases of coronary artery occlusion in the absence of these associated conditions. In such cases the hypertrophy has been interpreted as a direct consequence of the ischemia due to the coronary artery occlusion. This conclusion is based on evidence that cardiac hypertrophy may follow experimentally induced anemia and that it occurs in various clinical forms of anemia (p. 1049) and in cases of an anomalous coronary artery arising from a pulmonary artery and supplying the heart with relatively unoxygenated blood (p. 791). More direct evidence was adduced by Smith, Miller and Graber,[80] who observed the development of cardiac hypertrophy in dogs following experimental coronary artery ligation. Unlike these observers, Sutton and Davis[84] saw no change in the size of the heart in dogs following coronary artery ligation.

My own observations have led me to believe that when cardiac hypertrophy follows coronary occlusion it is due either to present or preexistent hypertension, to associated cardiovalvular disease or to congestive heart failure caused by severe extensive myocardial damage. Solival and I[8] studied the hearts at autopsy of 100 cases of acute coronary occlusion to determine the relationship of this condition to cardiac hypertrophy. Hearts with associated cardiac disease had been excluded. The cases with and without hypertension were segregated. Evidence of previous hypertension in patients with normal blood pressure during their final illness was sought in the records of previous hospital admissions or from their family physicians. Preexistent hypertension was also assumed to have been present if the examination of the fundus had disclosed severe arteriosclerosis and if postmortem examination disclosed advanced renal arteriolosclerosis of the interlobular arteries or arteriolosclerosis. The presence or absence of cardiac hypertrophy was based on the relationship of the heart weight to normal body weight and comparison of this figure with the normal figures of Smith.[81] This study disclosed that cardiac hypertrophy was absent in every case of acute coronary occlusion without evidence of hypertension or associated cardiovalvular disease, unless there were distinct clinical or pathologic signs of congestive heart failure. In the presence of congestive heart failure marked cardiac hypertrophy was noted whether or not there was associated

hypertension Within the hypertensive group cardiac hypertrophy was much more prominent when the hypertension was associated with failure than in the absence of failure Hypertension per se was accompanied by lesser degrees of hypertrophy than heart failure without hypertension

Davis and Blumgart[6] also noted the relationship of congestive heart failure to the occurrence of cardiac hypertrophy in a study of cases of heart failure not due to hypertension valvular disease or other accepted causes of hypertrophy In 14 of 15 cases of congestive heart failure associated with advanced coronary atherosclerosis the heart weights were above 400 gm and in 11 of these above 500 gm and in 5 above 600 gm On the other hand in 31 cases of advanced coronary heart disease without associated heart failure only 6 hearts weighed more than 400 gm and no heart weight exceeded 440 gm Davis and Blumgart concluded that the failure was the cause and not the result of the cardiac hypertrophy since otherwise they would have found some markedly hypertrophied hearts which had not yet failed

Although cardiac hypertrophy is seen pathologically and cardiac enlargement is observed clinically in many cases of coronary occlusion it is important to emphasize that the heart is often of normal size in this condition Horine and Weiss[36] reported 20 cases of acute coronary thrombosis followed roentgenologically for periods between five months and ten years in all of which the size of the heart was normal during the entire period of observation Miller and Weiss[51] studied 19 necropsied hearts with old cardiac infarcts none of which disclosed cardiac hypertrophy In a roentgenographic study of 200 patients with acute coronary thrombosis followed for an average period of three years Palmer[60] found 72 (36 per cent) to be of normal size Of those which were enlarged only 4 (2 per cent of the total series) were not associated with hypertension or other conditions which are accepted as causes of cardiac enlargement No mention was made of the possible role of congestive heart failure in these cases In a somewhat similar roentgenologic study of the hearts of 16 patients with acute coronary thrombosis Massie and Miller[47] noted no change whatever in the size or shape of the heart in 8 cases In the first two weeks following the acute attack an increase in heart size was observed in only 2 cases The absence of cardiac enlargement should therefore not depreciate a clinical diagnosis of acute coronary occlusion The presence of cardiac enlargement should merely suggest associated or complicating conditions

RECENT MYOCARDIAL INFARCTION WITHOUT ACUTE CORONARY OCCLUSION

Experimental and pathologic observations have revealed that coronary artery occlusion is not invariably followed by cardiac infarction because of the presence or development of collateral circulation It is less well known that areas of acute myocardial necrosis or infarction occur frequently in the absence of a recent occlusion of a coronary artery Isolated observations of this kind were noted by Libman Saphir et al[74] Buchner et al among others Friedberg and Horn[27] found that in a series of 1000 consecutive autopsies 31 per cent of the cases of acute myocardial infarction were not associated with a recent coronary artery occlusion All the coronary vessels were meticulously examined by transverse sections of the arteries at intervals of 3 mm and microscopic examinations were made of all extremely narrowed portions of the vessels In 37 such cases of acute myocardial infarction without recent coronary occlusion pulmonary embolism was associated in 12 calcific aortic valvular stenosis in 8 severe coronary and old occlusions with congestive heart failure in 6 an operative procedure in 4 a severe acute anemia in 3 malignant hypertension and a cerebral complication in 3 and occlusion of the superior mesenteric artery in 1

It is probable that myocardial infarction may occur whenever there is prolonged severe myocardial anoxia whether this be due to a mechanical occlusion or to other disturbances in circulatory dynamics which result in coronary insufficiency In the above cases of myocardial necrosis or infarction without recent coronary occlusion there were many factors which could result in a sharp inadequacy of the coronary blood supply for the needs of the myocardium Shock following operation or mesenteric thrombosis the fall in aortic and therefore in coronary blood pressure after a massive pulmonary embolism or acute hemorrhage could precipitate such a coronary insufficiency[21] In cases of calcific aortic

stenosis there is a progressive increase in intraventricular pressure with a diminished cardiac output and a deficient filling of the coronary capillaries (p 701) At the same time there is a greatly augmented need for blood because of cardiac hypertrophy and the increased work of the heart with this valvular lesion In most of the cases a severe narrowing of the coronary arteries or an old occlusion had already impaired the coronary circulatory reserve

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Chapter 20

ACUTE CORONARY OCCLUSION AND MYOCARDIAL INFARCTION

Clinical Features

SYMPTOMATOLOGY

PREMONITORY SYMPTOMS

Acute myocardial infarction presents itself usually as a sudden catastrophic incident, and its definitive clinical picture develops without warning prodromata. But numerous studies[18, 4, 181] disclose that preliminary chest pain may represent an harbinger of acute coronary occlusion in 10 to 50 per cent of the cases. Such premonitory pain usually develops within 24 hours prior to the occlusion, but it may precede the attack by several days or even weeks. Occasionally palpitation, weakness or dizziness may represent the premonitory symptoms, with or without associated pain.

The premonitory pain is usually identical with that of angina pectoris in character and location and in being often precipitated by exertion or emotional excitement. Of course such pain can be considered definitely a premonitory symptom only if the patient has not been subject to regular attacks of angina pectoris for many months or years, and if it is followed by the more definitive clinical picture of acute cardiac infarction within a few days or at most a few weeks. The absence of characteristic electrocardiographic changes and other objective evidence of myocardial infarction during the interval substantiates the concept that the pain is actually a preliminary symptom and not due to the infarction itself. In my own experience the most striking instances of premonitory pain have been observed in patients with previous myocardial infarcts and usually with angina pectoris on effort. In these patients a fresh coronary occlusion and cardiac infarct were often signalized by *increasing frequency and severity of* the episodes of angina pectoris which appeared with less and less exertion and even at rest or only in recumbency.

The pathologic basis for the premonitory pain may be a sudden narrowing of a coronary artery due to the rupture of intramural capillaries in an atherosclerotic plaque. The interval preceding the actual infarction represents the time required for the formation of a thrombus or hematoma sufficient to occlude the artery completely. It is more likely that the sudden appearance of premonitory angina pectoris actually corresponds to a coronary occlusion but that infarction of the heart muscle is delayed until exertion or some other factor, by enhancing the oxygen requirement of the *ischemic area* of heart muscle intensifies the myocardial anoxia and produces necrosis. Or else the occluding thrombus extends proximally to involve additional branches of the vessel which had been serving to maintain viability of the affected myocardium.

Recognition of these premonitory symptoms has been stressed because an early diagnosis of impending coronary occlusion may prompt immediate institution of rest in bed and other therapeutic measures. Whether such measures would actually diminish the mortality rate or the frequency of complications is unknown. However, since myocardial infarction does not invariably follow coronary occlusion immediately rest in bed by diminishing the work and oxygen requirement of the heart muscle might occasionally inhibit the development of myocardial infarction despite

the coronary occlusion and the administration of anticoagulants might inhibit extension of the coronary arterial thrombus

Desirable as these theoretical benefits might be in practice it is difficult to evaluate this preliminary pain except in retrospect after the full picture of myocardial infarction has unfolded Quite frequently identical pain and associated symptoms are later found to represent episodes of angina pectoris which are not followed by myocardial infarction On the other hand it is important to recognize that many episodes of anginal pain or so called premonitory pain actually represent attacks of myocardial infarction even when the classic symptoms of the latter are absent Such symptoms may be properly interpreted only when careful studies are made of the temperature white blood count sedimentation time and electrocardiograms

CLINICAL PICTURE OF ACUTE MYOCARDIAL INFARCTION

For purposes of presentation the clinical picture of acute myocardial infarction may be classified according to the following distinctive features

1 Cases dominated by pain
2 Cases dominated by shock
3 Cases dominated by pulmonary edema or other evidence of acute left ventricular failure
4 Cases characterized by the more gradual development or aggravation of congestive heart failure
5 Cases dominated by complications

Emphatically I do not intend to pose these groups as distinct entities most cases are characterized by a combination of the symptoms and signs listed under the various headings However one group of symptoms or the other often dominates the clinical picture and recognition of acute myocardial infarction will be facilitated by a knowledge of these varied and sometimes sharply different clinical forms that the disease may assume

1 Cases Dominated by Pain

In its most characteristic form the clinical picture of acute coronary occlusion with myocardial infarction is dominated by severe and prolonged pain in the region of the sternum the precordium or the upper abdomen [70, 87, 93] The victim is stricken while at rest or at work when awake or asleep with or without the dubious benefit of premonitory pain The pain may either begin as a relatively mild but persistent discomfort which becomes increasingly severe or it may strike with sudden terrifying intensity Often the subject has previously experienced paroxysms of angina pectoris But despite certain similarities of the pain of myocardial infarction to that of angina pectoris he often knows that this is a new and different pain The pain may appear distinctive because for the first time it attacks while he is asleep or at rest and without apparent cause Or if it arises during walking or other exertion it fails to subside promptly with rest If the patient follows his custom of taking nitroglycerin to dispel his anginal pain he discovers with alarm that this pain is not similarly alleviated

Character of the Pain The pain of acute myocardial infarction has the same quality of constriction oppression or compression which characterizes angina pectoris and it may be no more severe But often it is more crushing in intensity and becomes intolerable because of its prolonged duration Usually the pain is characterized as squeezing constricting choking vise-like or like a heavy weight but it has also been described as expanding stabbing knife-like dull and boring or burning in quality

Location and Radiation Almost always the pain is located in the retrosternal area Often it spreads to both sides of the anterior chest especially to the left A prominent component of the pain may affect the epigastrium or upper abdomen This accounts in part for the resemblance of myocardial infarction to acute surgical or chronic diseases of the abdominal viscera and for the frequency with which such cases were formerly diagnosed as acute indigestion

Like the pain of angina pectoris that of acute myocardial infarction radiates frequently to the shoulders and both upper extremities to the neck and jaw and to the interscapular region Radiation of the pain to the neck is often described as causing a clutching or choking sensation The pain in the upper extremities more often in the left may either extend continuously from the shoulder to the fingers or reach only to the arms or skip directly to the forearms or wrist There may be only a dull ache weakness or numbness of the wrists associated with severe substernal and precordial pain

Duration of Pain The pain persists in vary

ing degree for many hours, occasionally for several days

The duration of the pain is abbreviated frequently by the administration of morphine or some other opiate, but even opiates may hardly diminish the pain or at best leave a persistent dull ache or pressure With or without morphine the pain may not be constant even though prolonged After an hour or two of severe pain, the pain may lessen perceptibly or subside entirely only to recur for hours or days in irregular rhythm

In some cases there is intense pain for thirty minutes to one or two hours, thereafter the pain disappears completely and the patient may feel and appear perfectly well Only electrocardiographic studies may disclose that the pain was due to an acute myocardial infarction When a pericardial rub discloses the existence of an acute fibrinous pericarditis there may be no distinct change in the pain occasionally however a recurrence or intensification of pain suggests a relationship to the pericardial lesion or the precordial pain becomes intensified by deep respiration Sometimes there are two distinct types of pain a constant retrosternal pain characteristic of the myocardial infarction and a pericardial (pleuropericardial) sharp pain related to deep respiration

After the pain due to the myocardial infarct subsides the patient may become subject to paroxysms of angina pectoris whether or not he suffered angina pectoris prior to the acute attack These may occur while he is still in bed, as a result of slight *activity, meals or emotional states* More often angina pectoris develops only during convalescence, upon the resumption of activities out of bed On the other hand, patients previously plagued by frequent attacks of angina pectoris may be completely relieved of their pain after they recover from the acute myocardial infarction

Pathogenesis of the Pain of Myocardial Infarction The essential similarities in quality, location and radiation support the theory that the pain of myocardial infarction like that of angina pectoris is due to myocardial anoxia (p 457) In angina pectoris the pain is brief and paroxysmal because the myocardial anoxia is provoked only by certain activities or emotional states which are themselves transient The pain subsides with the cessation of the causative factor or after administration of a vasodilator like nitroglycerin, because the myocardial anoxia is reversible and there is no significant permanent anatomic change In cases of myocardial infarction the pain is prolonged because myocardial anoxia is usually due to mechanical occlusion of a coronary artery which is not transient or reversible, the artery is not capable of dilatation by nitrite In cases of myocardial infarction without coronary artery occlusion the causative factors produce a severe and prolonged myocardial anoxia sufficient to cause permanent myocardial damage

The greater severity of pain of myocardial infarction as compared to that of angina pectoris is probably an expression of more extensive or more intense myocardial anoxia, and of the longer duration The severity and persistence of the pain of myocardial infarction may be simulated during a paroxysm of angina pectoris caused by rapid walking if the patient forces continuation of his activity despite the pain The extension of the pain of myocardial infarction to the upper abdomen may represent an overflow of pain impulses to a wider area of neighboring segments of the spinal cord due to the severity and extent of the cardiac lesion However, occasionally this localization may be due to an associated acute pericarditis or perhaps occasionally to hepatic engorgement Aside from these considerations individual differences in pain sensitivity and in the pathways of conduction of pain from the heart (p 459) probably account for some of the variations in the severity, location and radiation of the pain of *myocardial infarction*

The eventual course of the pain is determined by the pathologic and physiologic changes in the ischemic area A variable central portion of the affected muscle undergoes complete necrosis and is no longer capable of causing pain, for the pain stems from anoxic but viable tissue The peripheral rim of ischemic muscle remaining viable may receive a completely adequate collateral blood supply from anastomotic vessels In that circumstance there may be no pain at all after the acute infarction even with exertion If the collateral supply is merely adequate to maintain viability but provides no reserve, this portion of the ischemic myocardium may become anoxic with effort or under other conditions which temporarily increase the oxygen need of the myocardium or diminish its blood

supply Then paroxysms of angina pectoris may follow recovery from the acute infarction

Myocardial Infarction without pain has been documented in a number of cases[44, 84, 111] In Bean's series[17] of 125 cases of acute myocardial infarction pain was noted in only 75 per cent but pain was absent in only 4 4 per cent of 974 cases of acute myocardial infarction and 226 cases of coronary insufficiency studied by Sigler[172] In an additional 2 9 per cent the pain was very mild and in 8 3 per cent the pain was elsewhere than the anterior chest Cases without pain have been described as silent or atypical[186] But usually these are characterized by the sudden development of pulmonary edema congestive heart failure shock or weakness features now recognized as intrinsic elements in the symptomatology of acute myocardial infarction Pain is said to be uncommon with acute myocardial infarction occurring in Negroes in whom dyspnea is the usual clinical manifestation[72] In a study of 70 cases of myocardial infarction without pain Evans and Sutton[68] found that preexistent heart failure or myocardial infarction as well as atrial fibrillation and hypertension increased the likelihood that pain would be absent in myocardial infarction These authors suggested that slowness of myocardial infarction rather than the size of the infarct determined the absence of pain

In many purported instances of acute myocardial infarction without pain I have been able to elicit a history of typical pain on requestioning the patient Often pain was not reported by the patient because it was overshadowed by dyspnea weakness or other symptoms Some patients who deny the presence of pain will admit that they experienced a clutching or gripping sensation a sense of strangulation or a feeling of a massive weight on their chests Pain may also be overlooked when it is relatively mild and of brief duration or forgotten if the diagnosis is made long afterward by electrocardiographic examination If those instances are omitted in which pain is overshadowed by other symptoms misinterpreted or forgotten only a small percentage of cases of acute myocardial infarction remain which were unaccompanied by cardiac pain Reports indicate that pain is absent in not more than 3 to 4 per cent of cases of acute myocardial infarction[28] and Babey[11] could find only one case without pain in a series of 116 In some of these painless cases coronary occlusion may have been followed by such prompt and complete ischemia of a portion of the myocardium that no pain could arise This is apt to occur when a previous occlusion has produced myocardial anoxia without infarction and the fresh occlusion leaves this portion of anoxic myocardium without any collateral blood supply Extreme shock following myocardial infarction may completely benumb the cerebral centers to the awareness of pain Finally hyposensitive individuals may experience no pain at all atypical radiation of pain or substitution symptoms instead of pain The latter include weakness dizziness syncope sweating or vomiting instead of the usual and characteristic pain[17] As most of these substitution symptoms are manifestations of shock there may be some question whether pain is absent because of the hyposensitivity of the patient or because it is overshadowed by manifestations of shock

2 Cases Dominated by Evidence of Shock

While some evidence of shock is often observed in the previous group of cases characterized by intense substernal pain there is a group in which the manifestations of acute cardiac infarction are *primarily* those of shock The patient suddenly experiences weakness which slowly or rapidly may develop into intense prostration or collapse He may unexpectedly slump in his chair if sitting or fall to the ground if standing or walking He may lose consciousness for a brief period probably because of cerebral ischemia due to the low cardiac output Syncope marked the onset of acute cardiac infarction in 10 of 200 cases studied by Cookson[44] In extreme cases shock may be followed by sudden death

In milder cases the patient may complain only of feeling weak dizzy faint or nauseated or less specifically of feeling sick These symptoms may be very transient and associated with a cold sweat Sometimes there is a terrifying inexplicable fear of impending doom angor animi out of proportion to the symptoms Vomiting is not uncommon and rarely diarrhea occurs The patient may complain of thirst

In instances of profound shock the subjective symptoms are associated with cold clammy extremities and tip of the nose a rapid weak or thready pulse pallor or grayish cyanosis and a low blood pressure (below 80

mm Hg) and low pulse pressure In attacks beginning with syncope there is often a bradycardia, but there may be a tachycardia [33] Respiration may be rapid and shallow, especially if there is some associated left ventricular (congestive) failure and sometimes there is frequent sighing The facial expression is often drawn and anxious The patient's intellect may be clear but often he is mentally befogged and apathetic The oral temperature may be subnormal, while the rectal temperature is elevated There may be a notable diminution in the urinary output and rarely complete anuria for 24 hours [148]

The advent of therapeutic agents which give promise of usefulness in the treatment of shock in acute myocardial infarction has pointed up the disagreement regarding the criteria of shock and consequent differences in the mortality rate in such cases of shock (p 564) For purposes of uniformity it appears desirable to formulate as minimal criteria for shock associated with myocardial infarction (1) a systolic blood pressure less than 80 mm Hg regardless of the previous pressure, (2) clinical manifestations secondary to diminished cardiac output and sympathetic vasoconstriction e g cold clammy skin, rapid thready pulse etc (p 302)

When shock occurs it usually evolves soon after the onset of myocardial infarction and lasts a few hours to one or two days In fatal cases it may persist longer and until the patient succumbs Often in such cases shock is accompanied by pulmonary edema If the patient recovers from the shock state, some *degree of weakness often persists The patient* may first become aware of other symptoms hitherto obscured He may complain of a pressure pain over the sternum or precordium, pain or weakness in the arms or forearms or numbness in the wrist or fingers Epigastric fullness gaseous eructations and other symptoms of indigestion may become annoying Sometimes subsidence of shock may be followed gradually by the emergence of signs of congestive heart failure In some cases shock may persist for one or two weeks especially when there is extensive or progressive myocardial infarction, or when complications such as embolization, arrhythmias or bronchopneumonia ensue

Pathogenesis of Shock in Acute Myocardial Infarction Most probably the symptoms of shock are due to the sharp and sudden reduction of the cardiac output resulting from myocardial injury [55 176 80] Observations that experimental shock occurred only after occlusion of coronary vessels of certain critical sizes were interpreted to indicate that some mechanism, probably neurogenic prevented a compensatory rise in peripheral resistance, with consequent fall in blood pressure [9] Shock due to cardiac infarction may sometimes be distinguished from that due to peripheral vascular failure by the frequent presence in the former of dyspnea and orthopnea and distention of the peripheral veins The degree of shock does not always correspond to the size of the infarct, for the extent of the infarct is not necessarily an accurate measure of the severity of the chemical and physiologic disturbances in the heart muscle Moreover, some nervous mechanism may be concerned the behavior of which varies in different persons

3 Cases Dominated by Acute Left Ventricular Failure

A sudden attack of pulmonary edema is often the first and may be the dominant manifestation of acute myocardial infarction The attack may appear suddenly and without warning causing thoracic oppression and intense, suffocating dyspnea and orthopnea Sometimes however, it follows hours or days after premonitory substernal pain or recovery from the earlier stage of shock

The respirations become noisy and asthmatic or bubbling in character A copious white or pinkish foam may be coughed up or merely wells up from the bronchopulmonary *passage and out of the oral cavity and nasal* passages Retrosternal pain may be absent or slight or if moderately intense it is usually overshadowed by the profound dyspnea and sense of suffocation Patients in this group may be deeply cyanotic or may present a pale or ashen cyanosis due to the combination of pulmonary edema with shock Particularly in elderly persons and in the presence of both shock and left ventricular failure or after opiates, there may be *Cheyne Stokes respiration*

Lesser grades of pulmonary congestion due to acute left ventricular failure are also common The onset may be characterized by episodes of paroxysmal nocturnal dyspnea The wheezing respiration and cough associated with diffuse bronchial rhonchi and distention of the chest may provoke a diagnosis of

bronchial asthma More commonly such episodes of cardiac asthma are associated with the characteristic pain of acute myocardial infarction or they appear after pain and evidences of shock have subsided *If myocardial* infarction begins with massive pulmonary edema the patient may succumb rapidly or if he recovers he may become subject to less severe left ventricular failure characterized by recurrent cardiac asthma orthopnea or dyspnea on slight exertion Cough with or without expectoration and hemoptysis may also be present Moist râles are usually audible at the base of the lungs and the second pulmonic sound may be accentuated

Since myocardial infarction affects the left ventricle almost exclusively it is not surprising that manifestations of left ventricular failure are common Sudden inability to expel the venous return results concomitantly in pulmonary congestion and in deficient cardiac output and shock Some evidence of pulmonary congestion as denoted by râles at the base of the lungs is very frequent whether the dominant manifestation is pain or shock or congestive heart failure

4 Cases Dominated by Manifestations of Right Sided Heart Failure

Although evidences of left sided heart failure usually combined with varying degrees of pain and shock are common even *with* the first acute myocardial infarction right sided heart failure develops rarely during the first attack and then only after the acute symptoms have subsided However with the second or subsequent infarction evidences of right sided congestive heart failure appear with increasing frequency and occasionally dominate the clinical picture The peripheral veins become engorged and the venous pressure elevated [171] Usually the liver becomes enlarged and it may be tender Peripheral edema may be present but usually ■ a late development Right sided heart failure after myocardial infarction is always associated with *left sided failure Dyspnea orthopnea and at*tacks of cardiac asthma usually persist but they are often at least partly alleviated with the development of right sided failure Basal râles are usually audible and the circulation time remains prolonged The symptoms and signs of right sided heart failure may emerge during the first week after myocardial infarction but usually they develop after many weeks as the patient ■ convalescing and resuming some degree of physical activity Sometimes rapid enlargement of the liver and peripheral venous engorgement may appear *within a few hours after the occurrence of* chest pain

There is in addition a group of cases in which a first attack of myocardial infarction is followed within a period of weeks or months by progressive and advanced right-sided heart failure with minimal or no apparent evidence of left sided heart failure The pathogenesis has been explained on the basis of ventricular septal infarction and a so called Bernheim ■ syndrome This explanation is *dubious*

Occasionally the development or intensification of right sided heart failure is the major or sole feature of an attack of acute myocardial infarction In most of these cases the patient is one who has had a previous attack of myocardial infarction following which he has continued to experience angina pectoris or paroxysmal and exertional dyspnea Then without characteristic symptoms of acute myocardial infarction the signs and symptoms of right-sided heart failure develop more or less rapidly over a period of days or weeks

Less frequently patients of middle or advanced age without previous cardiac symp*toms or evident cardiac disease* experience progressive dyspnea and display signs of left and right-sided congestive heart failure That these clinical manifestations are the result of a fresh myocardial infarct is demonstrated either by definite electrocardiographic changes or by pathologic findings at autopsy The occurrence of right sided heart failure after coronary occlusion is dependent on widespread myocardial damage which implies the existence of multiple or large infarcts fresh or old

5 Cases Dominated by Complications

Occasionally none of the above mentioned striking symptoms are present or they appear in such mild form that they are overlooked *The first conspicuous symptom* of acute myocardial infarction may be that of a complication whose relation to the cardiac infarct may or may not be recognized These complications which are discussed in detail below (p 510) include cerebral or other embolization and arrhythmias

Sometimes coronary occlusion results in prompt and *sudden death* in patients who may

or may not have suffered from angina pectoris or other evidences of coronary disease

ASSOCIATED AND MINOR SYMPTOMS

The clinical features of acute myocardial infarction have been depicted as distinct integral groups, but I reemphasize that the main symptoms of pain, shock and heart failure are usually associated in the same patient, although one or the other may predominate at different stages of the disease It should also be reaffirmed that quite frequently these symptoms do not appear in the striking form in which they have been described and that they are often mild in intensity and brief in duration Indeed it is probable that instances of myocardial infarction with mild symptoms of brief duration are more frequent than is generally recognized, for postmortem studies indicate that there are many more coronary occlusions than are or could be recognized clinically Many patients do not suffer severely enough to warrant the summons of a physician

There are many less specific accessory symptoms which accompany but are overshadowed by the major clinical features enumerated Sometimes when cardiac pain is relatively mild and evanescent and there are no distinctive symptoms of shock or congestive heart failure, these accessory or minor symptoms may dominate the clinical picture

Gastrointestinal Disturbances and Abdominal Pain

Symptoms classified loosely as "*indigestion*" occur so frequently that cardiac infarction was formerly often mistaken for an attack of acute indigestion Nausea and vomiting are common especially when pain is severe When the pain extends to the upper abdomen and is associated with vomiting the clinical picture may resemble that of cholelithiasis, acute cholecystitis, peptic ulcer or urolithiasis When there are also evidences of shock it may simulate a perforated ulcer or acute pancreatitis In other cases the pain is so obscured by the nausea and vomiting that the whole episode is attributed to a gastrointestinal disturbance It is probable that the nausea and vomiting are due to a vagovagal reflex from the region of the infarcted myocardium to the gastrointestinal tract Often it is uncertain whether vomiting which occurs only after the administration of an opiate is due to the opiate or to the disease itself

Diarrhea with or without vomiting is occasionally experienced at the onset of acute cardiac infarction probably also as the result of a vagovagal reflex More often *constipation* results from the diminished intake of food the administration of morphine or its derivatives and the stay in bed

Abdominal distention and a sense of epigastric fullness are common If the pain is not severe, they may dominate the clinical picture from the outset, but more often they become conspicuous after the pain has subsided Self medication with bicarbonate of soda or other alkalis or carminatives in an unsuccessful effort to relieve these digestive symptoms often precedes the patient's summons of a physician In some instances abdominal distention and constipation are intensified later in the course of the attack by gastrointestinal and hepatic engorgement due to the development of right sided heart failure

Jaundice has been noted rarely In at least one patient whom I observed the jaundice was due to a coincident obstruction of the common bile duct by a calculus

Other Symptoms

The occurrence of intense prostration or collapse due to shock has been mentioned but often only a moderate sense of *weakness* accompanied by cold perspiration and perhaps slight dizziness represents the total or dominant symptomatology of an attack Weakness is a common and conspicuous feature which persists long after most or all of the acute symptoms of cardiac infarction have disappeared It is especially common in patients who develop distinct signs of congestive heart failure, but it may represent the only or the chief residual symptom

Palpitation is a common complaint, especially after the more conspicuous symptoms have subsided It may become particularly annoying when it is associated with extreme tachycardia or other arrhythmia or when there is a sinking or fluttering sensation of irregular, premature or dropped beats

Urinary symptoms are rarely prominent but there may be a reduction or more rarely an almost complete suppression of the urinary output (p 520)

Cerebral symptoms are relatively uncommon except for the mental torpor or collapse as-

sociated with severe cardiac shock at the onset of the disease But occasionally they are the most impressive features of the disease while the coronary occlusion is unsuspected[19, 21] Mental torpor or confusion dizziness or vertigo loss of memory stupor or coma is likely to occur in elderly patients with cerebral atherosclerosis in whom the blood flow to the brain is further diminished by the sudden drop in blood pressure Hemiplegia and aphasia may result early from cerebral vascular thrombosis with encephalomalacia or hemorrhage or from cerebral embolization arising in ventricular mural thrombi Occasionally there are epileptic convulsions or delirium Attacks of convulsions and faintness or syncope (Adams-Stokes syndrome) may be due to complete heart block or episodes of ventricular fibrillation with resulting intervals of asystole and cerebral ischemia (p 390) Cheyne-Stokes respirations may appear especially in elderly persons with cerebral atherosclerosis or when intense cerebral ischemia results from extreme cardiac shock (for pathogenesis see p 198) The administration of opiates and the advent of left ventricular failure with consequent overventilation and acapnia may be important contributing or precipitating factors Coma may be due to a complicating diabetic acidosis

Other symptoms occur rarely *Hoarseness* due to the paralysis of the left recurrent laryngeal nerve may result from compression of that nerve by the engorged left pulmonary artery in left ventricular failure[11]

Hiccup has been noted occasionally[114] and has been attributed to associated diaphragmatic pericarditis with irritation of the phrenic nerve or to associated pneumonitis with diaphragmatic pleurisy

OBJECTIVE MANIFESTATIONS OF ACUTE MYOCARDIAL INFARCTION

GENERAL APPEARANCE AND BEHAVIOR

In the classic case characterized by severe pain the patient presents a striking contrast to the person suffering from a paroxysm of angina pectoris Although the pain is similar in quality and location the patient with angina pectoris usually remains utterly quiet fearful of every motion having discovered that rest relieves and activity kindles or intensifies the pain With the onset of pain from an acute myocardial infarction he may at first also try to remain motionless But with persistence and increasing intensity in the pain he becomes extremely restless Sometimes his futile efforts to relieve the pain lead to bizarre forms of behavior He may tear or clutch at his chest as if to remove a weight or release a vise-like band or he may massage it vigorously as one does a cramp in a leg He may thrash from side to side in an effort to find a comfortable position in bed or he may alternately get up and sit down or pace the floor as he moans with pain I have seen patients on the floor crouching on their knees as some do when suffering from a biliary or renal colic Occasionally a patient with acute cardiac infarction purchases some relief by extending his arms upward as if to enlarge the capacity of the chest He may be found lying in bed with his hands above his head clutching the head of the bedstead On one occasion I found a patient suspended by his hands from the top of a door As a rule however when the physician arrives the patient is found in bed where he is squirming restlessly holding his chest and complaining of pain

When shock is the predominant feature the patient s appearance is characterized by listlessness or prostration as he lies quietly in bed Although he may acknowledge the presence of pain he does not complain of it spontaneously His vocal responses in general are low and brief as if every word is an exhausting effort Occasionally he is somewhat confused and disoriented or he may appear dazed His countenance is of ashen pallor and his lips and fingertips faintly cyanotic His hands and feet and the tip of his nose are cold and moist There may be a bluish red mottling of the skin (cutis marmorata) On one occasion I have seen striking acrocyanosis of the fingers and toes From the beginning or as the shock clears after the first few days the patient s appearance is gradually modified by the intrusion into the picture of a variable degree of left-sided heart failure

A somewhat different appearance is presented by the patient whose attack of myocardial infarction is evinced predominantly by acute pulmonary edema He is found propped up high on several pillows gasping for breath his neck veins often engorged and his lips and skin distinctly cyanotic Between gasps he may complain of a massive oppression over the chest This may be described as a pain

but more often as a sense of suffocation He may express a fear of impending death He may cough occasionally, the sputum produced may be blood tinged In extreme cases there is a copious foamy pink stained fluid exuding from his mouth and sometimes even from his nostrils Frequently, moderate or severe shock is associated, then the cyanosis has an ashen hue, the extremities are cold and the peripheral veins in the extremities may be collapsed although those in the neck are tense The appearance described above may be observed only if the patient is seen soon after the inception of his symptoms Pulmonary edema often clears with remarkable speed either spontaneously or after an opiate, the morning after the attack the patient may appear quite comfortable or only moderately dyspneic and orthopneic In the more ominous cases however, pulmonary edema may persist for several days until the fatal end or disappear and recur several times until the patient succumbs

These, the most dramatic and most severe clinical pictures usually represent only the onset or first few days of the attack Some patients, appearing perfectly well, walk into the physician's office to report a pain that has already disappeared or dyspnea which disturbs them only at night or recently developed symptoms of indigestion Many others are sufficiently alarmed to go to bed and call a physician, but present no striking abnormalities in appearance or behavior as they complain of persistent chest pain and perhaps also weakness, perspiration nausea or abdominal distention or breathlessness

THE HEART

Physical examination of the heart often reveals surprisingly little in view of the extent and severity of the cardiac damage When percussion of the cardiac borders and palpation of the apical impulse are satisfactory, there is often no evidence of cardiac enlargement However, in the presence of congestive heart failure the heart may be so enlarged that this is readily determined by percussion and palpation

Auscultation of the heart may be more revealing although frequently this also discloses no significant abnormality In many cases the heart sounds are faint in volume and muffled in quality The first sound in particular is usually faint and low pitched It may be indistinguishable from the second sound, with a consequent tic tac rhythm A soft blowing murmur at the apex, probably due to a functional mitral insufficiency, is most often heard in instances of second or multiple infarction in which there is some degree of left ventricular dilatation An aortic systolic murmur may also be noted, its pathogenesis is uncertain but it is usually attributed to atherosclerotic changes in the ascending aorta near the aortic ring When hypertension persists despite the myocardial infarction, the second aortic sound may be accentuated or even reduplicated Often in cases characterized by left ventricular failure with pulmonary hypertension the second pulmonic sound is accentuated and may be louder than the second aortic sound, even when there is systemic hypertension

Gallop rhythm and pericardial rub have a more specific diagnostic value I have heard a gallop rhythm in one quarter of the patients whom I have been able to observe within the first few days after the onset of the attack Shillito et al [171] noted it in 8 of their 50 cases The gallop rhythm is usually best heard at or slightly medial to the apex of the heart, but it may be most clearly audible in the fourth interspace near the left sternal border Occasionally the gallop can be detected over a wide area of the precordium It is protodiastolic or presystolic in time, more frequently the latter if the ventricular rate is rapid

In their study of the heart sounds in 80 cases of cardiac infarction, Master and Friedman[107] noted an atrial sound in 83 per cent which was sufficiently accented in 33 per cent to produce an audible presystolic gallop In 47 per cent there was a third heart sound early in diastole, in 8 per cent this sound was accented and audible as a protodiastolic gallop In 6 per cent there was a superimposition of the atrial and third heart sound causing an audible summation gallop Thus there was an audible gallop in almost one half of their cases

Since gallop rhythm is probably associated with left ventricular dilatation (p 69), it is usually encountered in cases in which heart failure is significant Gallop rhythm most frequently appears in the first day or two after the infarction and disappears as cardiac function is adjusted But if conspicuous heart failure continues, gallop rhythm may

also persist Sometimes in cases with severe shock at the onset of the attack there is no audible gallop during the first few days But as shock subsides and left ventricular failure becomes more prominent gallop rhythm may become manifest

A *pericardial rub* has been noted in about one fifth of the cases in several reported series [22, 17] Undoubtedly it would be heard more often if it were deliberately sought and if patients were examined frequently soon after the onset of the attack For the rub appears intermittently persisting briefly at each appearance It may first be audible a few hours after the attack but most commonly on the second or third day thereafter it recurs usually only for a few days Occasionally with large infarcts or progressive myocardial infarction a pericardial rub persists continuously for many days

The pericardial rub is usually heard best just inside the apical impulse or along the left border of the sternum but it may be audible over a large part of the precordium or localized over the lower portion of the sternum A pericardial rub is not indicative of anterior infarction as is commonly believed it may be heard also following posterior ventricular infarction [184] It is much more likely to appear when there is a generalized acute fibrinous pericarditis than with a localized pericarditis and generalized pericardial inflammation may follow posterior as well as anterior wall infarction *In 3 out of 5 cases of generalized* pericarditis associated with an audible rub Stewart and Turner[186] found the infarcted area limited to the posterior wall

A pericardial effusion following myocardial *infarction has been reported rarely* [175] *It is* probably overlooked in most cases in which it occurs Nichol[1 5] reported a pericardial effusion sufficiently large to necessitate a paracentesis A pericardial rub may be audible even when the effusion develops A distinction should be made between pericarditis with effusion and a non inflammatory hydropericardium representing a serous transudate due to advanced congestive heart failure The pericardial effusion may consist of pure blood (hemopericardium) a consequence of cardiac rupture (For hemopericardium see p 604)

THE PULSE

There is usually an acceleration in the pulse rate to between 100 and 110 per minute especially during the febrile stage At the very onset the pulse rate may be rapid in the presence of shock or heart failure even when the temperature is normal In the absence of noticeable heart failure shock or fever the pulse rate is usually normal Occasionally there is a sinus bradycardia with a pulse rate of 60 per minute and rarely complete heart block with a pulse rate below 40 The rhythm of the pulse is usually regular but premature beats occur commonly and occasionally other arrhythmias may produce irregularity or a striking quickening of the pulse

THE BLOOD PRESSURE

As a rule cardiac infarction is followed by a fall in the blood pressure [188] But initially there may be a transient rise even when there are other clinical evidences of shock [184] The blood pressure usually falls further in patients with hypertension than in those with a normal pressure prior to the attack The eventual pressure may decline to 90 mm Hg or lower regardless of the blood pressure before cardiac infarction But patients with previous hypertension usually have higher pressure after infarction than those with previously normal pressure The diastolic as well as the systolic pressure is reduced but not to the same degree In consequence the pulse pressure is usually significantly diminished In contrast with these usual findings Yater et al [207] reported that the blood pressure remained *normal or returned to normal in 70 per cent of* soldiers between the ages of 18 and 39 who had survived an attack of acute coronary thrombosis

The fall in blood pressure usually occurs *rapidly sometimes after several hours* but more often on the second day of the attack Occasionally there is a gradual progressive decline and rarely it is delayed for a week [25] In early fatal cases often associated with blood pressures below 90 or 80 mm Hg there may be little or no rise in pressure up to the end But in most cases a low point is reached some time in the first week or more often in the second or third week [108] After one to three weeks at this level there is a gradual progressive rise However the blood pressure seldom returns quite to its initial level until after convalescence About two thirds of the patients with previous hypertension eventually regain their hypertension In some of these hypertension reappears within several

weeks or months after moderate activity is resumed but in others one to three years may elapse before the previous levels of high blood pressure are attained.[131] Occasionally I have observed the blood pressure dive precipitously on the first day after an acute coronary occlusion and rise sharply on the following day, almost but not quite to its initial level. In fatal cases the blood pressure may remain at its lowest hypotensive level until the patient succumbs.

The fall in blood pressure after acute myocardial infarction is probably related chiefly to the reduction in cardiac output although these two do not follow a uniformly parallel course. Compensatory vasoconstriction is an important modifying factor. This and the later recovery in cardiac output account in most cases for the subsequent rise in blood pressure and restoration to the original level. But in about one third of the patients with previous hypertension the blood pressure, after cardiac infarction, remains within a normal range for at least many months, even though there is no longer any evidence of a diminished cardiac output, and cardiac function appears well compensated. In these patients it must be assumed that the persistent diminution in blood pressure is due to a permanent relaxation in the peripheral arterial resistance.

FEVER

Usually within 24 to 48 hours, and occasionally as early as 4 to 8 hours after the onset of acute cardiac infarction, there is a moderate rise in temperature to 100 to 102 F. But fever up to 104° or 105° has been observed not infrequently. Shillito et al[171] noted fever at some time in all of their 50 cases of uncomplicated myocardial infarctions. The temperatures must be taken rectally and at regular intervals to discover slightly abnormal elevations.

The temperature usually reaches its peak on the third or fourth day and persists altogether for two to four days but occasionally longer. As a rule, the temperature returns to normal by the seventh or eighth day. However, progressive myocardial infarction or the development of complications may prolong the duration of the fever, or may cause a recrudescence if the temperature has already returned to normal.

LEUKOCYTOSIS

An increase in the white blood cell count occurs almost invariably and early, occasionally within two hours after the onset of the attack. Most frequently the leukocytosis is detected on the second or third day, but Slapak[173] found that the leukocytosis appeared on the first day, reached its maximum on the eighth day, and then fell rapidly. As a rule the white blood count varies between 12 000 and 15 000 but counts between 15 000 and 20 000 are not rare. There is an associated polynucleosis of 75 to 90 per cent and there may be a slight shift to the left, that is, the percentage of young (nonsegmented) forms is increased.

The leukocytosis recedes after a few days and usually disappears by the end of a week. Persistence of the leukocytosis thereafter or the presence of extremely high white blood counts suggests the development of a complication such as pulmonary or other embolism, bronchopneumonia or progressive myocardial infarction.[99] However, Levy[95] has observed a which they reported and Shillito et al[171] in 49 cated case of acute myocardial infarction.

The presence of a leukocytosis may be a valuable diagnostic aid in dubious cases of myocardial infarction. The white blood count is often a more sensitive index of cardiac infarction than the temperature because there may be a definite leukocytosis when the presence of fever is uncertain as in cases with a temperature around 100° F.[96] Furthermore, the leukocytosis usually develops before fever.

INCREASED SEDIMENTATION RATE

The rate of sedimentation of the erythrocytes is almost always increased following an acute myocardial infarction.[149, 141] Rabinowitz et al[146] noted this in all of the 29 cases which they reported and Shillito et al[171] in 49 of 50 uncomplicated cases of cardiac infarction. The increased sedimentation rate is attributed to a change in the composition of the plasma due to the absorption of products of the necrotic heart muscle.

Usually the increased sedimentation rate is first noted on the second or third day of the attack and persists for several weeks until the infarct is healed. The accelerated rate may begin within a few hours after the acute myocardial infarction, attain its most rapid phase in four or five days and persist for a variable

period of weeks or months. In the classic cases of acute myocardial infarction there does not appear to be a good correlation between the degree of increase in sedimentation rate and the severity of the attack or the prognosis.

SERUM GLUTAMIC OXALACETIC TRANSAMINASE (SGO-T) AMINOPHERASE

The enzyme glutamic oxalacetic transaminase (GO T) is probably present in all human sera and also in various tissues, particularly heart muscle, skeletal muscle, brain, liver and kidney in descending order of concentration. The normal serum glutamic oxalacetic transaminase (SGO T) concentration is 8 to 40 units per milliliter. Following acute myocardial infarction, the serum transaminase (SGO T) rises to 70 to 600 units in 12 hours to six days.[illegible, 77, 109a] It is presumed that the enzyme is released from damaged myocardial cells, since the concentration of GO T in infarcted myocardium is only 2 to 10 per cent of normal heart muscle.[17, 110] Following experimental coronary occlusion and myocardial infarction in dogs, serial serum transaminase determinations show a linear correlation between the peak level of SGO T and the amount of myocardial infarction.[3] But myocardial ischemia of 45 minutes' duration in dogs did not influence SGO T if there was no myonecrosis.[17] Following myocardial infarction in humans, the peak level of transaminase is usually noted about 36 hours after onset of the pain and the concentration usually returns to normal by the fourth day. Occasionally, however, the maximum rise in SGO T does not occur until after the third day, and in other cases the rise occurs early and is transient, with return to normal within 36 hours.[29] Hence it is important to measure the SGO T early and to do serial determinations. The SGO T may be determined by the method of Karmen et al.[77]

It has been suggested that serum transaminase determinations may prove useful as a clinical aid in the diagnosis of acute myocardial infarction[illegible] and in estimating the amount of myocardium involved. It is apparent, however, that SGO T will be elevated whenever there is necrosis of any transaminase-rich tissue, i.e., in acute liver damage (hepatitis), acute skeletal muscle damage including dermatomyositis, acute renal damage (renal infarction), and in rheumatic myocarditis. However, as a rule, it should be possible to exclude these other causes of elevation of the SGO T. Differentiation of myocardial necrosis and hepatic damage may be facilitated by the simultaneous determination of the activity in the serum of the enzymes glutamic pyruvic transaminase (SGP T) and lactic dehydrogenase (S LD).[159] SGP T rises sharply after hepatic damage and insignificantly after myocardial necrosis, whereas S LD activity increases after myocardial necrosis and is relatively unaltered after hepatic damage. Since serum glutamic oxalacetic transaminase (SGO T) is not increased following uncomplicated pulmonary embolism, its determination may be helpful in the differential diagnosis of pulmonary embolism and myocardial infarction.[63] The determination of SGO T activity has also been found useful in the diagnosis of acute myocardial infarction in cases in which the diagnostic electrocardiographic changes are obscured by those of left bundle branch block.[6] On the other hand, Denney et al.[26a] reported an incidence of 4.8 per cent false negatives among 95 patients with myocardial infarction and a significant elevation of the SGO T in half of their cases of acute pulmonary embolism. But the level is not as high in the latter and the peak is reached on the third to sixth day instead of the second.[130a]

C-REACTIVE PROTEIN

This is an abnormal serum globulin which appears in the blood in response to a variety of infectious, neoplasms and other disturbances such as rheumatic fever and arthritis (p. 836). A positive serum C-reactive protein was detected regularly in cases of transmural infarction, but not during the "premonitory phase" of coronary occlusion or in patients with so-called coronary insufficiency.[14]

WELTMANN SERUM COAGULATION BAND

Delaney and Keyes[34] observed a *shortening of the Weltmann serocoagulation band* in cases of myocardial infarction, beginning on the second or third day and reaching its minimum by the fifth or the seventh day. Healing of the infarct was associated with progressive extension of the coagulation band.

OTHER LABORATORY FINDINGS

The examination of the urine usually discloses no significant abnormality. In patients with hypertension, a faint trace of albumin

and occasional hyaline casts are often found These findings are also associated with the development of right sided heart failure

Glycosuria and *hyperglycemia* have been observed not infrequently in patients with and without a previous history of diabetes [32,48] In diabetics who are especially subject to acute myocardial infarction glycosuria may reappear during the attack if previously controlled by diet or insulin Occasionally an acute myocardial infarction may precipitate diabetic acidosis and coma with obscuration of its clinical picture Patients with these complications often succumb despite prompt and adequate treatment of the metabolic disturbance

The occurrence of hyperglycemia and glycosuria in patients without a previous history of diabetes has been explained as due to adrenal stimulation in shock to circulatory disturbances in the vegetative centers of the brain or to the development of a manifest diabetes in a latent diabetic as a result of the acute cardiac infarction Goldberger et al [6] supported the latter theory and refuted the assumption that the hyperglycemia and glycosuria were insignificant and transient These observers performed glucose tolerance tests repeatedly over a period up to thirteen months on 14 patients with acute myocardial infarction none of whom had a history of diabetes They concluded that 6 presented definite evidence of diabetes 4 yielded abnormal glucose tolerance curves and 4 normal curves In several instances hyperglycemia and abnormal glucose tolerance curves were absent soon after the attack and appeared months later The tendency for the curves to become more and more abnormal over a period of months led these investigators to conclude that the hyperglycemia was not transient and that it indicated latent diabetes in these patients

Oliguria sometimes of extreme degree has been noted in association with intense shock and there may be anuria for as long as 24 hours [67, 115] In other instances acute tubular nephrosis ("lower nephron nephrosis") develops and may be fatal These disturbances result chiefly from prolonged cardiac shock and a consequent reduction in blood flow through the kidneys Sometimes urinary retention results from an associated prostatic obstruction the symptoms of which are intensified by bed rest

Hematuria may appear as a consequence of renal infarction, secondary to emboli arising from left ventricular mural thrombi Unilateral hemoglobinuria has been reported [98]

Creatinuria may result from increased catabolism following myocardial infarction [1] Urobilinuria has been noted, usually in the third day [62]

Chemical examination of the blood may disclose a hyperglycemia, which has been discussed above Although this may denote latent diabetes, it should not in itself be interpreted as an indication for the administration of insulin

Azotemia appears occasionally and rarely the blood urea nitrogen may exceed 60 mg per 100 cc [179] It is usually associated with severe shock and other factors which cause oliguria Blood lactate, pyruvate and amino acids are slightly elevated [8]

The serum alpha 2 globulin was found to be markedly increased in patients in shock due to myocardial infarction [81] The plasma fibrinogen is also elevated and the severity of the disease and prognosis have been correlated with the degree of elevation [100] Cryoglobulins have been found in the serum [73] Accelerated coagulability of the blood has been detected by means of a heparin clotting time [155]

CIRCULATORY DYNAMICS IN ACUTE MYOCARDIAL INFARCTION

The Cardiac Output

Determinations by the Wezler Boeger method[65] and by the ballistocardiograph[178] showed a tendency to a reduction in the cardiac output either in the first two or three days or after the first two weeks More recently a reduction in cardiac output following acute myocardial infarction was determined by the method of cardiac catheterization using the Fick formula [144] and by the dye dilution method [84, 174, 80] Gilbert et al [80] in a study of 20 patients with acute myocardial infarction found the cardiac index reduced, usually but not invariably in proportion to the clinical severity of the disease The degree of reduction was most marked in patients with shock The cardiac index normally 3 2 liters/min /sq m of body surface area averaged 2 6 for those without heart failure or shock 1 9 for those with heart failure, 1 0 for those in shock and 1 8 liters/

min /sq m for the entire group of 20 Except in cases with very low cardiac outputs and shock the blood pressure is well sustained even when the cardiac output is diminished denoting over all arteriolar vasoconstriction

The venous pressure is frequently normal or low but may be difficult to determine in patients with severe shock in whom the veins are collapsed Most reports now indicate that the venous pressure tends to be elevated in the shock following myocardial infarction[176] In patients with right sided congestive heart failure the veins may be engorged and the venous pressure elevated In the study of Gilbert et al [80] the venous pressure averaged 13 cm water in the group without failure or shock 16 7 in those with heart failure and 21 5 in those with shock but there was considerable variation in each group and all the patients in shock suffered some degree of heart failure also

The Circulating Blood Volume

The plasma volume determined by the Evans blue method in patients with myocardial infarction and shock was found to be somewhat low by Agress et al [4] but this was not confirmed by Smith et al [178] or by Gilbert and his colleagues [80]

The Circulation Time

This is usually prolonged only in patients with heart failure or shock According to Gilbert et al [80] the circulation time is much more prolonged in patients with shock than in those with heart failure without shock

ROENTGENOLOGIC FINDINGS IN ACUTE CARDIAC INFARCTION

The roentgenographic examination of the heart often discloses no abnormality following acute cardiac infarction or only slight alterations due to previous hypertension

Disturbances in the pulsations of the left ventricle can often be ascertained by fluoroscopic examination and by kymography or electrokymography These disturbances result from the diminution or absence of contraction of the infarcted heart muscle or from its passive expansion during systole The following fluoroscopic abnormalities may be noted

1 Localized more or less extensive *absence of pulsation* along the left lower border of the heart (left ventricular contour)

2 Local *reversal of pulsation* of the left ventricle i e there may be a systolic expansion of one part of the left ventricular contour while the remainder contracts For orientation the observer may view the aortic pulsations Distention of the aorta marks the onset of ventricular systole In addition to the above abnormalities kymography may also disclose diastolic splintering denoted as marked irregularities during diastole

Several sources of error should be considered (1) In large hearts the apical region a frequent site of infarction may disclose no pulsation or even reversal of pulsation when there is no infarction A pericardial tumor may produce reversal of pulsation (2) Accurate fluoroscopic observation of the pulsations of the heart is often difficult especially when there is a large extrapericardial triangular shadow (due to a fat pad) (3) The apical and adjacent supra apical region normally contracts slightly later than the more basal portion of the left ventricular contour Thus may be misinterpreted as a reversal of pulsation Roentgenologic diagnosis is further hampered by the fact that most patients with acute myocardial infarction are too ill to be subjected to such examination The findings of absence diminution or reversal of ventricular pulsation in cases of myocardial infarction may be observed with old as well as recent infarcts and with posterior as well as anterior infarction

Other roentgenologic abnormalities may result from complications of myocardial infarction such as pulmonary congestion due to heart failure pulmonary infarction pneumonia and ventricular aneurysm Enlargement of the heart in coronary occlusion has been discussed above (p 504)

Calcification of a myocardial infarct rarely with bone formation may be observed roentgenologically[59] However cardiac infarction is not the only cause of myocardial calcification Calcification of the coronary arteries of mural thrombi in mitral stenosis or after cardiac infarction of the pericardium of cardiac aneurysms and of the mitral or aortic valves must be differentiated[18]

ELECTROCARDIOGRAPHIC CHANGES IN ACUTE CARDIAC INFARCTION

Acute cardiac infarction usually produces alterations of the electrocardiogram which when studied early and by serial examination at brief intervals are diagnostic of the disease

The electrocardiographic changes following cardiac infarction are determined not by the causative coronary occlusion as such but by the location extent and irreversibility of the consequent myocardial anoxia and necrosis When coronary occlusion occurs without infarction there may be no significant electrocardiographic abnormality despite the occlusion, or only transient RS-T depressions or inversion of T waves associated with temporary and reversible myocardial anoxia

The process of cardiac infarction is an active and changing one, during which the absolute and relative extent of necrosis and anoxia varies until healing occurs The progressive changes are documented by corresponding electrocardiographic alterations which differ according to the interval since infarction and the degree of healing This evolutionary nature of the electrocardiographic patterns is an important diagnostic feature After the infarct has healed the electrocardiogram may continue to disclose abnormalities suggestive of the occurrence and even of the localization of previous infarction but these changes are rarely as conclusive or striking as those accompanying acute cardiac infarction

Factors Limiting Electrocardiographic Diagnosis

In most cases of acute cardiac infarction the electrocardiogram discloses changes which not only are distinctive for this disease, but also reveal accurately the location of the area of infarction [12, 54, 78] However in a variable percentage of cases the electrocardiographic changes may not be typical of acute myocardial infarction or do not disclose its location under the following circumstances [1]

1 Multiple infarcts occur commonly The electrocardiographic changes produced by the fresh infarct may be neutralized by those of previous infarcts Or the multiple infarcts may produce diffuse myocardial damage the electrocardiographic representation of which is indistinguishable from that of other varieties of diffuse myocardial disease

2 The presence of a bundle branch block may obscure the electrocardiographic pattern of acute cardiac infarction (p 533)

3 When extensive pericarditis complicates acute myocardial infarction, the electrocardiographic changes may be dominated by and diagnostic of acute pericarditis (p 534)

4 The number of electrocardiograms taken may be insufficient or the time at which these are taken in relation to the occurrence of the infarct may be improper to disclose characteristic changes

5 Previous treatment by digitalis produces RS T and T wave changes which may conceal those of myocardial infarction

6 The position of the heart in the thorax, i e a decidedly transverse or vertical heart, by its effect on the electrocardiogram may obscure the localization of the infarct

7 Electrocardiograms taken shortly before the death of the patient may fail to disclose the typical electrocardiographic changes of myocardial infarction

Typical Electrocardiographic Patterns in Standard Leads

The earliest changes affect the RS T segments[136] *and are usually observed within 24* hours rarely within a few hours after the attack [8] In some instances the ST changes appear only after two or three days or longer However according to the experimental observations of Bayley and associates [14] a primary inversion of the T wave may precede RS-T segment deviation

The first significant abnormality is an elevation of the RS T segment above the iso electric level in lead I or lead III or in precordial leads Characteristically this segment presents a "high take-off" from the descending limb of the R wave and its slope is convex upward [133] This elevation is transient lasting usually a few hours or days but it may persist for two to three weeks The upward convexity of the RS T segment often remains after it reaches the isoelectric level

Subsequent changes[136, 137, 8] produce a progressive regression of the ST segment to the isoelectric level and a concomitant lowering and eventual inversion of the T wave in the same lead (Fig 100) Simultaneously there is often a conspicuous and sometimes broad Q wave in the same lead [133]

Parkinson and Bedford [137] and Barnes and Whitten [■] observed that the changes in the ST segments and T waves fell into two common patterns which they designated as the T_1 and T_3 types Subsequent studies of the initial ventricular complex[136, 138] enlarged these patterns into the Q_1-T_1 and the Q_3-T_3 types A correlation of electrocardiographic and necropsy findings demonstrated that the Q_1-T_1 pattern was associated with an acute or healing infarction of the anterior wall and the Q_3-T_3 pattern with an acute or healing infarc

tion of the posterior or diaphragmatic wall of the left ventricle

Theoretical Basis of Electrocardiographic Changes in Acute Myocardial Infarction[11, 15, 78]

RS-T Deviations When myocardial infarction ensues after an acute coronary occlusion a central core of muscle undergoes necrosis and therefore produces no electrical phenomena This dead tissue is surrounded by a concentric shell of injured tissue which is still alive and therefore partially polarized[15] The injured tissue in turn is surrounded by ischemic tissue which may be normally polarized in diastole but which experiences a delay in repolarization during systole During the acute stage of infarction the injured tissue which is negative relative to ischemic or normal tissue gives rise to a persistent current of injury Normally during the transition from depolarization to repolarization i e during the RS T interval there is electrical neutrality and the RS T segment is on the base line (i e the isoelectric line) In myocardial infarction the current of injury directed toward the endocardium causes a negative or depressed ST segment in electrodes overlying the injured area But in standardizing the electrocardiogram we introduce a positive compensating current from the control battery to bring the string up to the base line by neutralizing the current of injury during diastole[15] When all of the normal muscle is depolarized (electrically negative) and the injured area is electrically negative the positive compensating current is unbalanced and produces an elevation of the ST segment In cases of anterior wall infarction with subpericardial injured tissue the leads whose exploring electrode faces the injured tissue (left arm lead I and precordial leads) show an elevated RS T segment A posterior wall infarct is associated with RS T segment elevations in leads facing the posterior wall of the left ventricle namely aV$_F$ lead III or II and III and the esophageal lead On the other hand leads facing away from the infarcted area may show RS T depressions or no deviation In a similar manner one can explain the occurrence of ST depressions in epicardial or precordial leads when the infarcted tissue is subendocardial since the current of injury now flows toward the epicardium and the compensating current is negative

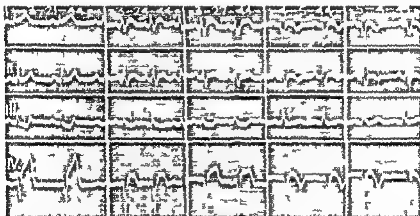


Fig 100 Acute coronary occlusion Anterior wall infarction Progressive changes R T elevations in leads I and IVF with depression in lead III Subsequent T wave inversion Absence of initial deflection (presence of Q waves) in IVF and lead I

The explanation for RS T deviations in acute myocardial infarction is uncertain and there are other explanations besides the one indicated above[111] Thus during the completely depolarized state i e the RS T interval the electrically negative injured tissue may be less negative than the depolarized normal tissue hence it conveys positive electromotive forces to the overlying electrode producing an elevated ST segment Or the injured area may actually be positive throughout systole including the S T interval when the normal muscle is isoelectric

According to vectorcardiographic theory the sum of electromotive forces in a heart with an acute infarct is not zero during the RS-T interval as it should be normally when all muscle is completely depolarized This is

owing to the persistent current of the injured muscle Hence the vector loop of the QRS does not return to its starting or zero point and the loop is open A line drawn from the zero point to the termination of the loop represents the vector of the RS T segment, indicating its direction and magnitude In infarction of the outer layers of the myocardium this vector is directed toward the epicardium Hence an elevated RS T segment is recorded in the electrode overlying the injured wall of the left ventricle

T Wave Changes *The ischemic area*, in contrast with the injured area, is believed to modify only the process of repolarization and is responsible for T wave changes including inversion[14] When the ischemic area is very large and the injured area absent or small, T wave changes may occur without ST deviations Normally T waves are upright in leads facing the epicardium if repolarization proceeds from epicardium to endocardium With myocardial infarction, negative T waves are thought to occur because repolarization proceeds from the normal subendocardium toward the injured subepicardial layer Hence in anterior wall infarcts T waves are likely to be negative (inverted) in precordial leads and leads I and aV_L In posterior wall infarcts leads aV_F (and II and III) have their exploring electrodes facing the ischemic areas and show inverted T waves but there are no T wave inversions in precordial leads In fact the absence of the normally counterbalancing electrical forces of the infarcted posterior wall *causes greater positivity of both R and T* waves in the right-sided precordial leads According to Dressler and Roesler,[4] high T waves precede inversion of the T waves or RS-T deviations The high T waves are believed to be part of the injury pattern possibly *due to the release of potassium from the* cells

Q Waves The dead infarcted tissue gives rise to no current If it extends transmurally it may be considered as a window cut out of the ventricular wall[197] Therefore the negative potential within the endocardial cavity is transmitted through this dead tissue to a superjacent precordial lead Instead of the normal positive initial deflection, the initial ventricular complex is downward, i e there is either a deep Q wave or QS in a lead placed directly over the infarct Or more commonly there is a deep or broad Q wave representing cavity negativity transmitted through the necrotic area, followed by an R or r wave representing depolarization forces of normal subepicardial tissue adjacent to the infarct

With healing of infarction, Q waves often persist in the precordial leads because a core of dead electrically inert tissue remains On the other hand, the injured tissue either dies, becomes ischemic or recovers and the RS T deviation therefore disappears The persistence of T wave changes depends on the presence of ischemic tissue of significant size, *thus causes aberrations in the repolarization process*

According to vectorcardiographic theory, the normal electromotive forces during depolarization and repolarization become unbalanced by the loss of electromotive forces of the injured infarcted tissue which was rendered electrically inert The direction and magnitude of the sum of the electromotive forces (i e, the cardiac vector) from moment to moment is therefore altered Normally, the initial and early vectors during depolarization are directed entirely toward the epicardial surface of the left ventricle or are so directed after a very brief moment away from that direction Consequently exploring electrodes facing the left ventricular epicardium show a major upward deflection (R) or a major upward deflection after an initial downward deflection of small magnitude (qR) Following subepicardial or transmural myocardial infarction the loss of electrical forces of the infarcted tissue unbalances the net sum of cardiac electromotive *forces in favor of* those directed away from the inert, injured tissue Therefore, an electrode facing the epicardial surface of the portion of the left ventricle which is injured has an early prominent negative or Q wave Thus in anterior wall *infarcts, there is a loss of anteriorly* directed electromotive forces which would normally be generated by the injured area The resultant forces are therefore directed away from the precordial electrodes and there is consequently a predominant negative or Q wave in the precordial leads

According to the theory of Prinzmetal and associates[80, 143, 147, 170] based on their studies of intramural leads the subendocardial layers are electrocardiographically inert during depolarization or are depolarized too rapidly to record on the electrocardiogram *Intramural* leads from the subendocardial layers give a

QS deflection identical with that from the cavities of the heart instead of the rS complex expected according to classic electrocardiographic theory Prinzmetal et al believe that subendocardial infarcts do not alter the QRS complex since they contributed nothing to this complex normally Their studies indicate that abnormal Q waves (coronary QR waves) occur in myocardial infarction of the outer layers of the wall when these layers contain both living and dead muscle They observed QS waves in transmural myocardial infarcts leading to a window effect[109] but also when there was through and through infarction with islands of living myocardial tissue[34]

These observers also found that the current of injury responsible for ST deviation was generated in injured tissue in the outer myocardial layers whereas injury to the inner layers produced ST segment deviations too small generally to be registered by clinical electrocardiography ST elevations diminished in amplitude from the epicardium to the endocardium and from the center to the border of the injury There is thus a gradient of positivity toward the epicardium and toward the center of the injured muscle accounting for ST depression on the wall opposite the injury They also observed a type of primary ST depression which occurs commonly at all stages of myocardial infarction and is usually noted in islands adjacent to infarcts

The changes seen in the standard or unipolar limb leads depend on the location of the infarcted injured or ischemic tissue the position of the heart and the relation of the latter to the sites of attachment of the extremities to the trunk If the injured and infarcted zone reaches the epicardium of the anterior wall there is a Q wave and an elevation of RS T in leads I and V_L which face the injured area and a depression of RS T in leads III and V_F and V_R facing the relatively normal tissue In posterior wall subepicardial infarcts Q waves and elevation of the RS T segment appear in leads III and V_F and in esophageal leads at the level of the ventricle Ex In pericarditis with universal subepicardial involvement of both walls RS T elevations occur in all standard leads since they all face the injured area But Q waves are absent since there is no transmural dead tissue In subendocardial injuries all standard leads usually face normal tissue which is interposed between them and the injured tissue therefore ST depressions may be seen in all these leads and there are no Q waves due to dead tissue

According to the electrocardiographic localization in one series of 974 cases of acute myocardial infarction the infarct was anteroseptal in 67 anteroseptal and anterolateral in 341 anterolateral in 117 posterobasal in 395 posterolateral in 21 and anterior and posterior in 33[112]

Anterior Wall Infarction (Q_1 T_1 Pattern)

The Q_1 T_1 type of electrocardiogram is characterized as follows (Figs 100 101)

1 At first there is an *elevation of the ST segment in lead I* and sometimes also in lead II with a simultaneous depression of ST in lead III (discordant ST deviations) Occasionally ST depressions only or high T waves may precede these discordant changes

2 The ST_1 elevation appears characteristically convex upward or dome-shaped with a downward slope toward the T wave

3 *The T wave in lead I subsequently becomes depressed or diphasic and eventually sharply inverted and V shaped* The limbs of the T wave may be symmetrical and the shoulders rounded upward At the same time the T wave in lead III becomes upright and sometimes exaggerated and sharply peaked (discordant T waves in leads I and III) The T wave deflection in lead II is usually similar to that in lead III but occasionally is inverted as in lead I

4 An early frequent change is the appearance of a *prominent Q wave in lead I* The Q wave may be broad It is followed usually by a low R wave with or without a subsequent S deflection This may produce an *M or W* shaped QRS in lead I There may also be a *definite Q wave in lead II* S_2 and S_3 are often conspicuous There may be a tendency to right deviation of the electrical axis

5 After two to four weeks but often in a few days the ST elevation in lead I is very slight or disappears but it may retain its upward convexity which slopes sharply downward toward an inverted T wave (coronary T wave[135] cove plane T wave[136]) The T wave may become upright in a few weeks but more often after three to six months or longer or may remain inverted

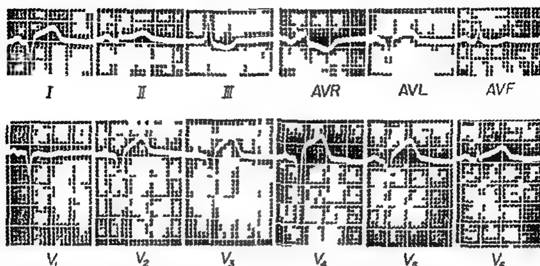


Fig 101 Acute myocardial infarction anterior wall *Q* waves and *ST* elevation in leads *I* and aVL as well as precordial leads

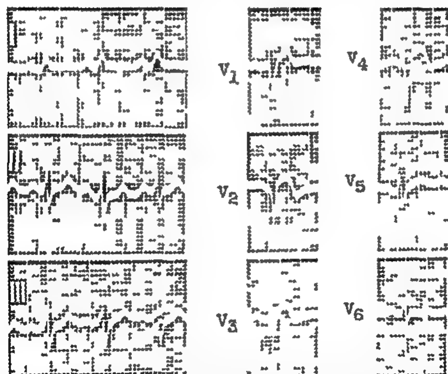


Fig 102 Acute anteroseptal infarction Characteristic changes of acute infarction absent or indefinite in standard limb leads Q waves RT segment elevations and diphasic T waves in V_{1-4} overlying anteroseptal wall with relatively normal QRST complexes in V_5 and V_6 overlying apex or anterolateral wall

Precordial leads[204, 197] may reveal characteristic changes when there is no abnormality in the standard leads or when the latter disclose only suspicious changes (Fig 102) They also localize the infarct more distinctly

1 There is an *early elevation of the ST segment* (more than 2 mm) Often the ST segment has a characteristic upward convex shape The ST elevation usually disappears in a few days but occasionally persists much longer

2 From the onset, or as the ST segment declines, there appears a *large initial negative deflection* (*Q wave*) (more than 2 mm) in lead of the normal initial upward deflection This

may be the sole deflection (QS) of the QRS group if so it is frequently slurred or notched in its descending limb Or else the deep Q may be followed by a much smaller R wave and occasionally also by a very small S wave In the latter instance the QRS may appear M or W shaped

3 As the elevated RST segment declines *the T wave becomes diphasic and then inverted* The inverted T wave is often large and sharply peaked Unlike the RS T elevations which are quite transient the T wave inversion usually persists for months and occasionally for years before reverting to normal or it may be permanent

Depending on the extent and location of the infarct these changes will be observed in one two or more of the precordial leads The presence of an abnormal Q wave may be due to either a recent or an old infarct A negative T wave in precordial leads is usually abnormal except in V_1 or V_2 and in children but it does not denote myocardial infarction unless serial electrocardiograms previously disclosed elevation of the RST segment and progressive T wave inversion The combination of an abnormal Q and a negative T is strongly suggestive of a previous or recent anterior wall infarct But in the presence of a normal R wave a negative T wave may be due to left ventricular strain or axis deviation RS T segment elevations and T wave inversions even without Q waves may denote acute myocardial infarction if there are serial changes Even then a definite diagnosis depends also on a compatible clinical history Serial changes in the T waves only may be suggestive of acute myocardial damage but then also a diagnosis of myocardial infarction is dependent chiefly on the clinical history As a rule infarcts causing only T wave changes are of small size and in unusual locations relative to the leads concerned

Subendocardial Infarction In some cases of typical clinical myocardial infarction subsequent pathologic examination discloses extensive necrosis confined to the subendocardial region and due to left or right coronary occlusion or extreme stenosis In such cases there may be no Q waves or ST segment elevations For ST segment elevations depend on subepicardial infarction and Q waves on through and through (transmural) infarction Instead there are striking ST depressions in all the standard leads and the precordial leads Thus electrocardiographic ST depression alone may signify serious or fatal cardiac infarction and should not be interpreted necessarily as denoting only reversible coronary insufficiency or coronary failure Furthermore ST depressions may be the initial electrocardiographic abnormalities before the classic findings of transmural infarction (Fig 103) Levine and Ford [*] on the basis of 6 proven cases of subendocardial infarction suggested as clues to the diagnosis ST depressions in precordial leads RS T elevation in aV_R and absence of prominent Q in aV_F

Occasionally there are *deeply inverted* T waves in one or more of the precordial leads from V_1 to V_6 and usually deepest in V_3 These findings were related frequently to subendocardial myocardial infarction in the anterior or lateral wall of the left ventricle [145] It was postulated that the T wave changes might be due to a transmural region of myocardial ischemia overlying a subendocardial zone of myocardial infarction [145] Similar T wave inversions may occur in patients with angina pectoris or with left or right ventricular hypertrophy pericarditis acute right ventricular dilatation anteroseptal ischemia or a small intramural or subepicardial infarct [116 146]

Anteroseptal Infarction An infarct localized in the anteroseptal region may be indicated by the following changes in unipolar precordial leads[1 0] (Fig 102)

1 An abnormal QR occurs in leads V_1 and V_2 or in one or more of V_2 V_3 or V_4 with a normal initial R in V_1 A Q wave may be considered abnormal if it exceeds one quarter of the height of the following R wave or it is prolonged more than 0 02 second from onset to nadir

2 There may be an elevation of the RST segment in leads V_1 or V_2

3 There are no abnormal Q waves in V_5 or V_6

Occasionally the Wilson type of right bundle branch block is the only sign of slight anteroseptal infarction [133]

Standard limb leads usually show no significant abnormalities as they are perpendicular to the direction of the advancing excitation wave and current of injury

If the entire septum is involved from anterior to posterior surface the electrocardiogram may disclose signs of anteroseptal infarction in precordial leads and of posterior

infarction in standard leads[183] Extensive septal infarction[1, 9, 183] may be suggested by (1) the occurrence of bundle branch block or severe atrioventricular block in the course of an acute myocardial infarction (2) the finding of Q waves in the right precordial leads in the presence of complete right bundle branch block, or (3) the finding of Q waves in left precordial leads in the presence of left bundle branch block

Anterolateral Infarction When small infarcts are localized to the lateral portion of the anterior wall, the presence of a Q wave and associated abnormalities in the RST segment and T wave might be limited to precordial leads taken from the fourth, fifth and sixth positions and be absent in positions further to the right

Lateral Wall Infarction (Posterolateral Apical lateral, Basal lateral, and High lateral)

Wood Wolferth and Bellet[98] described electrocardiographic changes which they believed were associated with infarction of the lateral wall of the left ventricle These consisted of depression of RS T in leads I and II absence of signs of infarction in lead III and depression of RST in lead IV Thomson and Feil[187] found 19 cases of infarction of the lateral wall (9 recent) in 106 necropsied cases of cardiac infarction In 4 of the 9

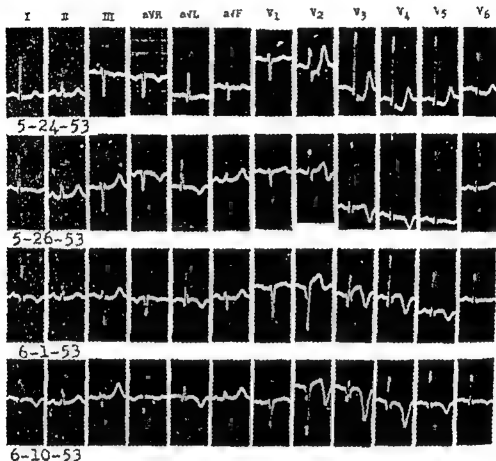


Fig 103 Evolution of electrocardiographic changes from subendocardial ischemia or infarction to transmural infarction (Courtesy Dr E Gipstein)

5-24-53 Substernal constricting pain requiring morphine Normal temperature and sedimentation rate (ESR) ST depressions in precordial leads suggesting so-called coronary insufficiency

5-26-53 Recurrent substernal pain at rest, radiating to back and arms Temperature and ESR normal T waves inverted in I aVL V_2-V_6

6-1-53 Deep Q wave and ST elevations V_2-V_3 cove plane deeply inverted T waves all denoting anterior wall myocardial infarction

6-10-53 Progressive changes of myocardial infarction

recent cases the electrocardiogram presented a pattern resembling that described by Wood et al [06]

In 6 cases of suspected infarction of the basal portion of the lateral wall of the left ventricle Rosenbaum Wilson and Johnston[154] found no unequivocal evidence of infarction in the standard precordial leads However distinctive changes were observed in unipolar leads from points on the lateral surface of the upper left thorax In another study of 105 cases showing lateral wall infarction at autopsy Myers et al [1 1] discovered electrocardiographic changes in one group like those described under anterolateral infarction In another group of cases representing a lateral

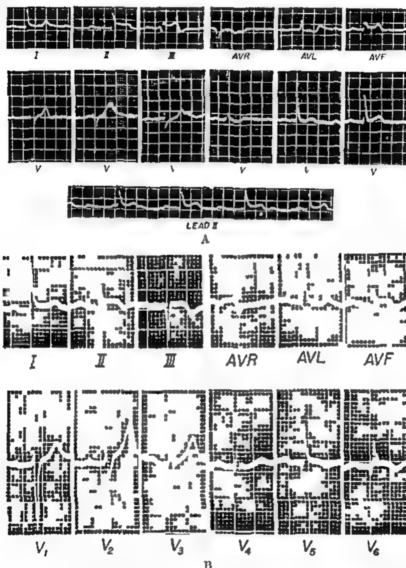


Fig 104 *A* Forty nine year old man Angina pectoris 2 years Premonitory pain 2 days Severe pain 9 hours 2 14 56 Electrocardiogram shows infarction of posterior wall of left ventricle with complete heart block T waves upright in precordial leads

B 2 15 56 Anterolateral extension of posterior wall infarct Q waves RT segment elevation and cove plane inverted T waves in V_5 and V_6

extension of a posterior infarct (posterolateral infarct) the lateral extension could be diagnosed from V_5 V_6 or V_7 and posterior infarction from V_E[119] (Fig 104*B*) The posterior portion of the infarct was most commonly undiagnosed when there was counter

clockwise rotation and a horizontal electrical axis of the heart conversely the commonest cause for failure to diagnose the lateral portion of the infarct in aV_L was clockwise rotation and a vertical electrical axis Primary lateral infarcts near the apex revealed abnormalities in V_5 V_6 and V_L, those near the base disclosed abnormalities in V_L and leads high in the left lateral thorax but uncommonly in V_5 or V_6 Q waves are most significant, while RS-T elevations or depressions depend on the subepicardial or subendocardial localizations of the infarct In high posterior infarcts ST depressions and/or tall R and T

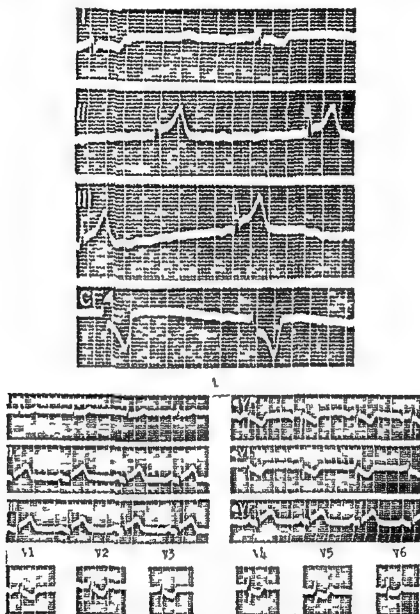


Fig 105 Posterior wall infarction A One half hour after onset R T elevations in leads II and III and R T depressions in leads I and CF_4 Tall broad T waves Atrial fibrillation
B One day after onset Same case Sinus rhythm Small Q_2 and Q_3 now present R T elevations in unipolar limb lead from left foot (aV_F)

waves in the precordial leads may be the sole changes

As a rule one should consider lateral infarction when deep Q waves and RS T elevations and T wave inversions are noted in aV_L and less regularly in V_6 or V_7 There may be a

prominent R and a shallow S wave in V_1[34] and in aV_R owing to the unbalanced electromotive forces away from the injured lateral ventricle and toward the right precordial leads Horizontal projections of the vector cardiogram in such cases show the vector loop strikingly displaced to the right.[47] In high posterolateral infarction Tulloch[188] has described findings significant of infarction in aV_L and in I, a predominant R in V_1 high upright T waves in two or more precordial leads ST depressions in V_5 and V_6 with elevations in leads V_7 to V_9

Posterior Wall (Diaphragmatic) Infarction (Q_3 T_3 Pattern)

1 There is an *early elevation of the ST segment in lead III and usually also in lead II* At the same time the ST segment in lead I is depressed (discordant ST deviation) (Figs 104 105)

2 The ST_3 elevation has a characteristic upward convexity or dome shape beginning at its high take-off from the R wave and sloping downward toward the T wave (Fig 106)

3 *The T wave in lead III and usually also in lead II becomes progressively lower diphasic and eventually sharply inverted and V shaped* The T wave in lead I is upright and often sharply pointed (Fig 106)

4 There is often an *early appearance of a conspicuous Q wave in lead III and often also a smaller Q wave in lead II* The Q wave in lead III may be the sole initial ventricular deflection or there may be a small R or small R and S waves In lead II Q R and S are often all of small amplitude producing a W or M shaped configuration A similar configuration in lead III is usually not significant There may be a tendency to left deviation of the electrical axis The presence of a Q_3 and inverted T_3 in themselves may not signify myocardial infarction for they may be produced by a transverse position of the heart The significance of a Q_3 is enhanced if S is absent in lead I[189] The presence of a deep Q wave in V_F strongly increases the probability that the Q_3 is due to posterior infarction and not to a semitransverse or transverse position of the heart[1] (Fig 105B) A Q wave in aV_F is probably indicative of posterior infarction if its voltage is 40 per cent or more of the voltage of the entire QRS in that lead (which must exceed 0 7 millivolt) and if the duration of Q is 0 04 second or more and is associated with an inverted T[110] Left ventricular hypertrophy may produce a Q wave and inversion of T in V_F

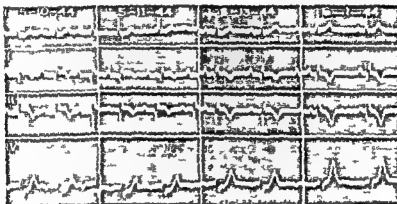


Fig 106 Posterior wall infarction Progressive changes

The *precordial leads* in cases of posterior (or diaphragmatic) wall infarction are not usually of diagnostic importance The following abnormalities may be observed (Fig 107)

1 Early and transient depression of the ST segment This is not as prominent as the elevation observed in instances of anterior infarction The ST depression is most likely to occur in true posterior wall infarcts not in farction of the diaphragmatic surface

2 An extremely *tall T wave* may appear (above 12 mm) Tall sharply pointed T waves in leads V_1-V_3 have been noted in the earliest electrocardiographic changes[190]

An esophageal lead at the level of the ventricles may disclose more striking changes including presence of a Q wave RS T elevation and T wave inversion[1 5 1 7] In posterior

basal infarcts only a unipolar lead over the xiphoid process may reveal the Q and RS-T changes of infarction. But there may be reciprocal RS-T depressions in V_1 to V_4. In high posterior (posterobasal) wall infarcts no Q waves may be inscribed in conventional leads and the electrocardiogram may appear relatively normal (see Vectorcardiogram, p. 535).

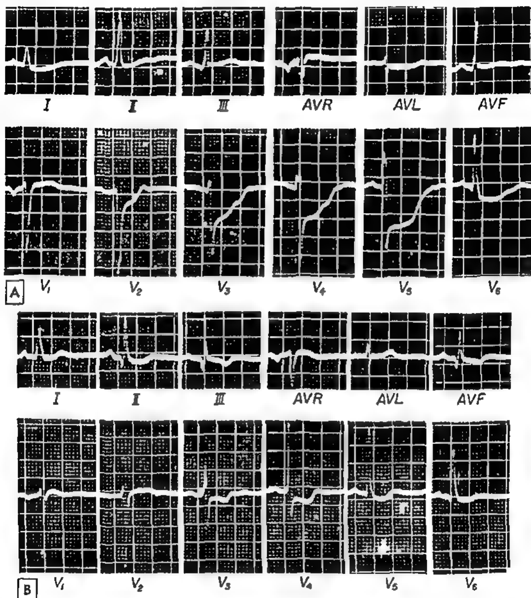


Fig 107 *A* Seventy year old man. Operated on for strangulated inguinal hernia. Angina pectoris 2 days preoperatively. Shock and pulmonary edema 4 hours postoperatively when this electrocardiogram was taken. Extreme ST depressions in all precordial leads (interpreted as "coronary insufficiency"). Slight ST depression in I and aV_L.

B After 10 days of progressive changes: Q wave, slight RT elevation and inversion of T wave in lead III and aV_F indicative of posterior wall infarction. Progressively less ST depressions in precordial leads.

Combined Anterior and Posterior Infarction

In combined infarcts of the anterior and posterior walls of the left ventricle the electrocardiogram may disclose patterns which include elements of the Q_1T_1 and of the Q_3T_3 type, or changes representing defective intraventricular conduction or bundle branch block, or nonspecific QRS and T wave changes. Occasionally one observes at the onset changes suggestive of a posterior wall infarction with subsequent development of a pattern of anterior wall infarction, or vice versa. When there is an old infarct on one surface and a

fresh infarct on the other the changes due to the recent infarct may be added to or may replace those of the previous infarctions [9] Thus Q waves in leads II and III may be residua of an old posterior infarct while RS-T *changes with subsequent inversion of* the T wave in lead I result from a recent anterior infarct The standard leads may disclose the Q_3-T_3 pattern of a posterior infarct while the precordial leads reveal the additional presence of an anterior infarct The V_F lead may be helpful [113] Often however an *acute* anterior infarct tends to conceal the electrocardiographic changes of posterior infarction [97]

ert the negative potentials of the right ventricular cavity are transmitted to the left precordial leads and Q waves appear Although Q waves are usually absent when left bundle branch block complicates anterior wall *infarction there may be a reduction in the* voltage of the R wave and elevated ST segment elevation in left precordial leads [11]

With *right bundle branch block* and a *posterior wall infarct* the characteristic electrocardiographic changes of the latter may be visible in the limb leads while the right bundle branch pattern is most distinctive in right precordial leads (Fig 108)

With *right bundle branch block* and an *an*

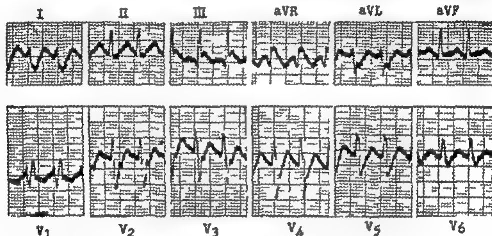


Fig 108 Posterior wall myocardial infarction with right bundle branch block in a diabetic woman 65 years old Posterior infarction indicated by Q and RT elevation in lead III Electrocardiogram per se compatible also with pulmonary embolism and acute cor pulmonale

Acute Myocardial Infarction with Bundle Branch Block [177, 13, 197]

In left bundle branch block the left ventricular cavity remains positive until the impulse from the right bundle branch crosses the septum The usual Q wave due to transmission of left cavity negativity to the exploring electrode over an infarct does not occur because of the positive left cavity potential An exception is a complete left to right infarction of the septum

With *left bundle branch block* the diagnosis of myocardial infarction is usually precluded except with extensive septal infarction [197] Owing to the left bundle branch block the left cavity potentials are positive and therefore the Q waves representing transmitted negative cavity potential in transmural infarcts are not present But if the entire septum is also infarcted and electrically in

terior wall infarct the presence of the latter may be obscured in the standard limb leads Significant Q deflections are absent but there may be an RT segment elevation with or without inversion of the T wave in lead I or I and II [11] The presence of the anterior infarct is revealed clearly in the precordial leads, which disclose the classic Q wave RS T elevation and T wave inversion (Fig 109)

Sometimes bundle branch block in the course of acute myocardial infarction is of transient duration Serial electrocardiograms may then disclose the characteristic changes of acute infarction in both the limb and precordial leads at those times when bundle branch block is not present The Wilson type of right bundle branch block may appear as a transient phenomenon in light anteroseptal infarction Occasionally, when the electro-

cardiographic changes of acute myocardial infarction are obscured by those of bundle branch block there may be sporadic interpolated premature ventricular beats which reveal characteristic changes of infarction [41]

Less Specific Electrocardiographic Changes

Dressler[40] has noted that at certain stages of acute myocardial infarction and sometimes during the period of preliminary pain an electrocardiographic pattern in which T_1

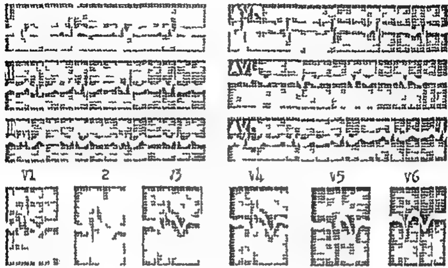


Fig 109 Anterior wall infarction with right bundle branch block Wide QRS complex with broad S in standard leads and catt n of right bundle branch block Anterior wall infarction disclosed by Q waves and RT elevations in precordial (V) leads

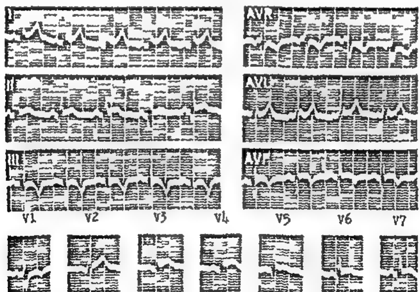


Fig 110 Acute posterior wall infarction with pericarditis RT elevation in leads II III and aVF with characteristic convexity upward Cove-plane T wave inversion and Q waves in leads III and aVF indicate posterior infarction The RT elevations with concavity upward in lead I and in precordial leads without Q waves suggest pericarditis

Myocardial Infarction and Pericarditis

In cases of acute myocardial infarction with diffuse pericarditis both the pericarditis and cardiac infarction may produce distinctive changes (Fig 110) For a differentiation between the electrocardiogram in pericarditis and acute myocardial infarction see p 598

is lower than T_3 is indicative of an anterior wall infarction This is especially significant when the patient is over 40 years of age and has been subject to attacks of angina pectoris In young persons rheumatic heart disease is more commonly responsible for this picture Normally T_1 is taller than T_3 except

when the heart has a vertical position when there is pulmonary emphysema or rarely in the presence of congenital heart disease thyrotoxicosis uremia, vitamin deficiency and trichinosis This pattern in which T_1 is smaller than T_3 is also associated with an old myocardial infarct Consequently a consideration of the clinical history is essential to determine whether this pattern signifies recent or old cardiac infarction

Characteristic elevation of the RS T segment with inversion of the T wave in lead I is strongly suggestive of anterior wall infarction even when the classic reciprocal RS-T depression in lead III is absent or inconspicuous Absence of the reciprocal ST depressions may be due to a simultaneous posterior wall infarct Similarly in cases of anterior wall infarction the RS T segment elevation in lead I may be inconspicuous or absent and T_1 may be only flattened or isoelectric but the reciprocal ST depressions and prominence of the T waves in leads III and II may be striking Sharply inverted V shaped T waves alone may appear in the standard leads after acute myocardial infarction but these findings in themselves are not diagnostic of the infarct

In some cases the significant finding is the low voltage (less than 0 5 mv or 5 mm) of the QRS complex in all leads with or without inverted T waves Often the QRS complexes are not only of low voltage but slurred and notched and they may be widened beyond the normal limit of 0 1 second These findings are associated with both fresh and old infarction as well as other conditions but in some instances with the aid of the clinical history and previous electrocardiograms it may be possible to conclude that the infarct developed recently Similar significance may be attached to an M or W shaped QRS of low voltage in leads I or II when interpreted in the light of clinical data

The P wave may be increased in amplitude and occasionally it is notched and widened Master[104] observed a P wave of 2 mm or more in at least one lead (usually lead II or leads I and II) in 40 per cent of his cases of acute coronary occlusion and attributed it to enlargement of the left atrium Bloom and Gilbert[21] observed a higher incidence of arrhythmias and conduction disturbances in those cases with large or notched P waves than in those with normal P waves The occurrence of conduction disturbances and arrhythmias in the electrocardiograms seen after acute myocardial infarction is discussed below

Although the electrocardiogram of acute myocardial infarction is usually distinctive patterns appearing in a variety of conditions (left or right ventricular hypertrophy bundle branch block potassium disturbances and myocarditis) may be mistaken for those of myocardial infarction[116 ...] See pp 462 3

VECTORCARDIOGRAM IN MYOCARDIAL INFARCTION[163 ... 6 203 195 201]

Consistent vectorcardiographic patterns delineating acute myocardial infarction cannot be presented because of persistent disagreement as to basic concepts of vectorcardiography and differences in method[162] of electrode placement Nevertheless it is claimed that myocardial infarction is one of the conditions in which vectorcardiography is diagnostically superior to electrocardiography

Myocardial infarction renders a portion of the myocardium electrically inert In consequence this muscle tissue fails to contribute its electromotive forces to the summation cardiac vector and the balance of forces is altered This disturbance affects predominantly the initial and early portions of the spatial vectorcardiographic QRS loop Abnormalities are indicated by changes both in the spatial orientation and in the direction of inscription of these initial and early forces of the QRS Such abnormalities as cannot be explained on the basis of position and rotation of the heart may be attributed to myocardial disease Changes in the initial portion of the loop are due to damage of the septum those in the very early portion of the loop to injury to the free wall of the left ventricle

Myocardial infarction during the acute phase is indicated also by failure of the loop to be closed the line drawn from the point of onset to the point of conclusion of the loop representing the ST vector Abnormalities in the T loop also occur

Septal Infarction The *initial* forces of the QRS *are oriented to the left and upward* instead of as normally to the right anteriorly and very slightly upward Usually this is combined with infarction of neighboring portions of the anterior wall (Fig 111)

Anterior Wall Infarction The early forces of the QRS are oriented posteriorly instead of anteriorly[6 ... 78a] there is clockwise inscription instead of counterclockwise in the frontal loop

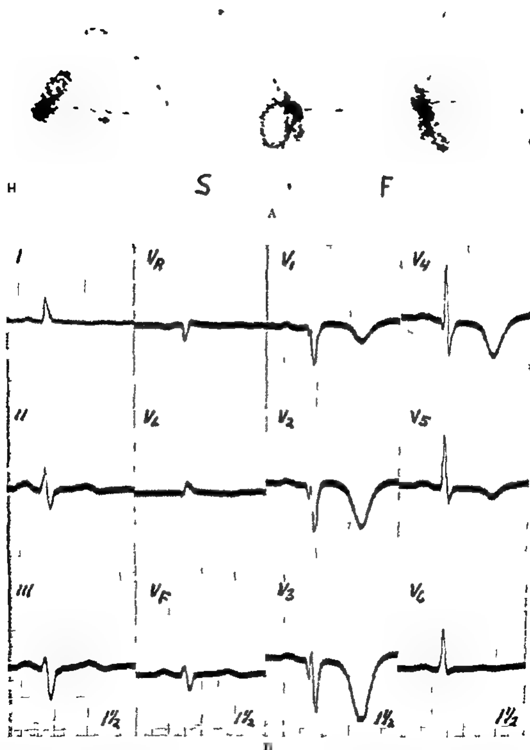
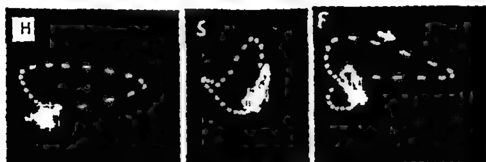


Fig 111 *A* Vectorcardiogram in anteroseptal infarction characterized by loss of initial deflection which is *normally directed anteriorly and to the right Therefore absence of R waves in right precordial leads of electro*cardiogram QRS loop inscribed sharp posteriorly and to the left in the horizontal plane
B Electrocardiogram of same patient



A

B

Fig 112 *A* Vectorcardiogram indicating infarction of diaphragmatic wall of left ventricle Normal QRS loop in horizontal plane but inscribed superiorly in frontal and sagittal planes with consequent absence of R waves in leads V_F II and III

B Electrocardiogram in same case

projection The entire loop may be oriented posteriorly

Diaphragmatic (Inferior) Wall (Fig 112) The early forces are directed upward and the major loop is displaced superiorly The inscription of the loop is usually clockwise in the frontal and counterclockwise in the sagittal projections both the reverse of normal But a horizontally lying loop which is inscribed clockwise in the frontal projection may represent ventricular hypertrophy

Posterior Wall Infarction The QRS loop is deviated anteriorly owing to loss of electromotive forces which are directed posteriorly The loop is inscribed clockwise in the frontal projection and counterclockwise in the sagittal projection both the reverse of normal Burch et al [6] using the tetrahedron reference frame, observed a characteristic upward displacement of the early portion of the QRS sÊ In high posterior infarctions which may not produce significant abnormalities in the conventional electrocardiogram the vectorcardiogram (tetrahedron or cube coordinates) shows a characteristic alteration of the loop to a rounded rather than oval form, the initial forces are markedly anterior and the rotation is clockwise instead of counterclockwise in the horizontal plane [illegible]

Lateral Wall The initial forces are normally oriented, but the early forces continue to the right because of a loss of the leftward forces of the lateral wall of the left ventricle If the posterolateral wall is involved the early forces are directed anteriorly and to the right, if there is a *high* posterolateral lesion the early forces are directed downward as well as anteriorly and to the right

In addition to the above changes in the variously located infarcts during the acute stage the QRS loop is open The previously described alterations in the QRS loop account for the presence of Q waves in various leads of the electrocardiogram the open loops for the ST deviations The direction of the vector from the zero point to the end point of the loop varies according to the location of the infarct being directed anteriorly to the left and upward in anterior wall infarcts, and posteriorly, downward and to the right in posterior wall infarcts The T loop often becomes long and narrow and is oriented opposite to the ST vector and points away from the infarcted area

When *left bundle branch block* occurs, it alters the entire vectorcardiographic QRS loop and precludes the diagnosis of associated myocardial infarction But in the presence of right bundle branch block of the Wilson type the occurrence of an infarct is indicated by changes in the initial or early portions of the QRS loop, whereas the bundle branch block is characterized by a slow inscription and abnormal orientation (to the right and anteriorly) of the terminal appendage of the loop

THE BALLISTOCARDIOGRAM[illegible]

Severe abnormalities of the ballistocardiographic pattern, graded II or worse by the criteria of Brown et al [illegible] are regularly observed during the acute stage of the disease In those who recover progressive improvement in the pattern usually occurs and may continue up to 8 months Serial ballistocardiograms were found by Mandelbaum and Mandelbaum[10] to provide a reliable index in determining myocardial functional recovery and prognosis with regard to resuming gainful activities

CARDIAC ARRHYTHMIAS IN ACUTE MYOCARDIAL INFARCTION

Premature contractions (extrasystoles), usually of ventricular origin, constitute the most frequent arrhythmia associated with acute myocardial infarction Rarely, multiple premature ventricular contractions presage the onset of ventricular tachycardia (see below)

All other arrhythmias combined appear much less often than premature contractions perhaps in about 15 to 20 per cent of cases of acute myocardial infarction They usually develop in the first three days of the attack but in occasional cases at any other time in the first two weeks Most of the arrhythmias subside spontaneously in 4 to 24 hours

Atrial fibrillation is next in frequency to premature ventricular contractions, whereas atrial flutter is observed less commonly [illegible] Atrial fibrillation often appears in the first few days and disappears spontaneously after several hours For this reason it is easily overlooked Occasionally, however, one of these paroxysms is the onset of persistent atrial fibrillation

Atrial or nodal tachycardia has been encountered in 0 5 to 2 0 per cent of cases [9] It may persist for several weeks

Ventricular tachycardia occurs rarely but may preface ventricular fibrillation and death. For this reason its prompt recognition and treatment are essential (p. 374).

Heart Block. Various grades are not infrequent (Fig. 113). The *prolongation of the P-R interval* was observed by Master et al.[106] in 16 per cent of 375 cases of acute myocardial infarction. In addition partial and complete heart block were noted in 3.2 per cent of their cases. Bean[17] observed a P-R interval of 0.2 second or longer in 30 per cent of his cases.

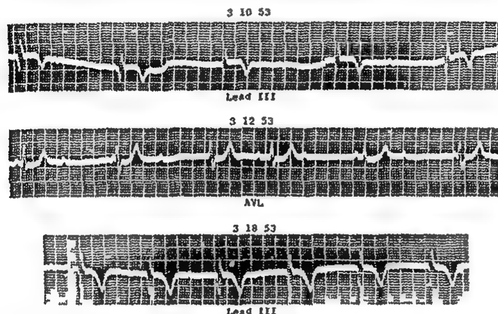


Fig. 113. Varying degrees of heart block with acute myocardial infarction, posterior wall.
3-10-53. Complete heart block; atrial rate 65, ventricular rate 34 and regular. P-R interval varies.
3-12-53. High degree of partial heart block with intermittent conducted beats. First and fifth ventricular complexes are sinus beats; second, third and sixth nodal beats; and fourth a fusion beat.
3-18-53. First degree heart block with prolongation of P-R interval to 0.48 second. Atrial rate 54, ventricular rate 54. P-R interval constant.

The prolongation of the P-R interval appears early, usually in the first week and often on the first or second day of the attack. However, occasionally it is observed only after several weeks. Decided variations in the length of the P-R interval may suggest that the process in the heart muscle is both recent and active. Bundle branch block and other intraventricular conduction disturbances are found more frequently in cases of cardiac infarction with a prolonged P-R interval than in those with a normal P-R interval. Usually the prolongation of the P-R interval persists several weeks and disappears. Occasionally it remains permanently, differing in this respect from other arrhythmias which rarely persist after myocardial infarction.

Partial heart block with Wenckebach period and dropped beats occurs occasionally. Both partial and complete heart block occur early in the attack and they may represent the first or only indication of an acute coronary occlusion. *Complete heart block* with atrioventricular dissociation has been considered very uncommon, but Schwartz[155] reported personal observation of the surprisingly large number of 15 cases. According to Kerr,[8] complete heart block occurs in only 2 to 3 per cent of cases of acute cardiac infarction and all forms of conduction disturbance in 7 to 8 per cent. As a rule heart block occurs early in the attack (Fig. 101). It is usually persistent but may disappear. The occurrence of heart block is almost always associated with occlusion of the right coronary artery, which in 90 per cent of hearts supplies the a-v node and the bundle of His through its ramus septi fibrosi. Since this branch arises almost at the origin of the right coronary artery, proximal to the usual site of thrombosis, the blood supply through this vessel to the node and bundle of His is only infrequently suppressed

But a subsidiary supply to the bundle comes from the left anterior descending coronary artery by way of its ramus limbi dextri. Because of a rich anastomosis between the left and right coronary arteries in the region of the a-v node and bundle, complete heart block is most likely to develop when both arteries have been occluded. If heart block appears after an acute anterior infarction (left coronary artery occlusion), it is probable that the right coronary artery was previously occluded. In most cases of heart block, autopsy examinations reveal multiple coronary occlusion with massive cardiac infarction, usually involving the interventricular septum. As a result, impaired intraventricular conduction (as denoted by wide and notched QRS complexes) is often associated with complete heart block.[169] Sometimes complete heart block is the result of damage and interruption of both bundle branches and not of the main bundle of His.

Adams Stokes syndrome (p. 390), This is characterized by convulsions, syncopal attacks and coma, may appear after the development of complete heart block,[169] but usually only when the ventricular rate falls below 40. Thus the incidence of the Adams-Stokes syndrome after acute myocardial infarction is much lower than that of complete heart block. Cookson[33] observed 5 cases of syncope or convulsions in the course of 200 cases of acute cardiac infarction. Two had syncope and 3 the complete Adams-Stokes syndrome including convulsions. In one instance an electrocardiogram taken during the attack showed complete heart block with the rate falling from 100 to 34. These attacks may also result from periods of ventricular tachycardia or ventricular flutter and fibrillation, which culminate in ineffectual cardiac systole and consequent cerebral ischemia (p. 377). In some instances, paroxysms of Adams-Stokes syndrome result from ventricular standstill following supraventricular or ventricular tachycardia or partial heart block. In cases with Adams-Stokes syndrome complicating cardiac infarction, other abnormal rhythms are common between attacks. Cookson[33] found posterior ventricular infarction in 4 of 5 cases of this type, in the other the site of infarction was undetermined.

Bundle branch block and other intraventricular conduction defects (p. 395) are fairly common, but only recognizable electrocardiographically.[168] These disturbances usually appear early and persist. However, I have seen bundle branch block appear with the onset of acute myocardial infarction and disappear as the more classic cardiographic features of this condition emerged. But when the bundle branch block persists, it often obscures the electrocardiographic features of myocardial infarction. Right bundle branch block may conceal a small anteroseptal infarct, both occurring simultaneously because the right bundle branch and the myocardium involved receive their blood supply from the ramus limbi dextri of the left anterior descending artery. Intraventricular and atrioventricular conduction defects may be associated.

COMPLICATIONS AND CAUSES OF DEATH

Shock and Acute Left Ventricular Failure

These occur so frequently with acute myocardial infarction that they have been discussed as intrinsic features of the disease rather than as complications. Either of these may be sufficiently severe to cause death within the first few days after the onset.

Chronic Left Ventricular Failure

This may develop gradually, weeks or months after the occurrence of acute myocardial infarction. Under these circumstances it is characterized by recurrent episodes of nocturnal dyspnea, a progressively increasing dyspnea on exertion, orthopnea, cough and the presence of rales at the bases of the lungs. Death may result from an acute attack of pulmonary edema. Often the symptoms of acute left ventricular failure subside after the first few days or weeks. In many cases chronic left ventricular failure persists for several years and the patient eventually succumbs to increasing left- and right-sided congestive heart failure or some other complication.

Right Ventricular Failure

This may appear after the acute symptoms of myocardial infarction have subsided. Patients with these symptoms may run a slow downhill course or die more or less suddenly. Together, left and right ventricular failure with or without shock constitute the chief cause of death from acute myocardial infarction.[49]

Embolization

Pulmonary, cerebral and peripheral emboli constitute the next most common cause of

death although such emboli are not always fatal Garvin[59] observed that in about 60 per cent of the cases of myocardial infarction that he studied there were one or more infarcts (presumably due to embolism) in the lungs brain *kidneys, spleen extremities and/or* intestine In a review of cases reported in the literature Hellerstein and Martin[49] found an average of 11 5 per cent of embolism or infarction In their own autopsy series of 160 cases 73 or 45 per cent were associated with embolism which was the main cause of death in 12 per cent and a contributory cause in an additional 15 per cent The frequency and importance of thromboembolic lesions in acute myocardial infarction has gained increasing significance recently because of treatment with anticoagulants

Pulmonary Embolism[15, 114] Pulmonary embolism is the most frequent of these embolic complications of acute myocardial infarction and is a commoner cause of death than is generally recognized Eppinger and Kennedy[49] found pulmonary emboli in 23 per cent of 200 cases of myocardial infarction proved at autopsy and emphasized the significance of pulmonary embolism as a cause of death Massive pulmonary emboli in accounted for 10 per cent of 577 deaths in somewhat more than 1000 cases of acute coronary occlusion studied by various observers[133, 49, 114] As a rule pulmonary emboli originate from peripheral thrombi in the veins of the lower extremities unlike the other forms of emboli which originate in mural thrombi in the left ventricle or atrium

Thus pulmonary emboli may be only in part a direct consequence of the cardiac infarction and slowing of the peripheral circulation bed rest and the associated venous stasis are probably more important causes This consideration is important in the treatment of acute myocardial infarction Although mural thrombi associated with myocardial infarction are located almost always in the left ventricle[159] they may also form in the right ventricle when there is extensive infarction of the interventricular septum In the latter circumstance the pulmonary emboli may be generated from a mural thrombus but this is a much less frequent source than the peripheral veins and the resulting emboli are less likely to be as large or as serious In still other cases in which there is *marked cardiac dilatation associated with right sided heart failure* mural thrombi may develop in the right atrium and may promote pulmonary emboli

Pulmonary embolization may *occur within the first few days after the onset of myocardial infarction but usually not until the* end of the first week or during the second week of the disease The emboli tend to recur each new embolus increasing the probability of a fatal outcome These episodes of recurrent emboli are usually misinterpreted as repeated fresh coronary thromboses Pulmonary embolization may occur while the patient is still bedridden, but frequently it develops suddenly when the patient sits up in bed strains at stool or gets out of bed for the first time

Cerebral emboli are probably the next most *serious form of embolization and like other* emboli to the systemic arteries originate in left ventricular mural thrombi Dozzi[33] in a review of 1000 consecutive necropsies found that in 12 (29 per cent) of 41 cases of coronary thrombosis there was an associated cerebral vascular accident Cerebral infarction was found in 5 to 15 per cent of various series of cases of myocardial infarction proven at autopsy[15, 49, 46] The clinical features may overshadow or obscure the more classic features of myocardial infarction Cerebral emboli usually result in encephalomalacia which may be evidenced by aphasia *hemiplegia* convulsions and psychic disturbances while the underlying myocardial infarction is unsuspected[50, 31] Occasionally such emboli are responsible for or contribute materially to the fatal outcome

Visceral emboli usually affect the kidney and spleen and occasionally the intestinal tract They may produce renal infarction with or without lumbar and ureteral pain and hematuria, *splenic* infarction usually asymptomatic but sometimes denoted by local pain on respiration and a splenic rub due to perisplenitis and rarely intestinal infarction with acute abdominal symptoms

Peripheral Emboli Embolization of the aorta at its bifurcation (saddle embolus), of the iliacs of the popliteals and of other peripheral arteries has also been noted Usually the embolus lodges at the bifurcation of a peripheral artery The most common site is the femoral at the origin of the profunda femoris and next most common are the common iliac, axillary and brachial popliteal and aorta in *that order*[1-8] Peripheral embolism is charac

terized usually by acute and excruciating pain, blanching of the affected area of skin, loss of sensation, coldness of the extremity, loss of arterial pulsation and later loss of motion of the affected muscles. Eventually these emboli may result in gangrene of the extremity but when located distally in the lower extremity or in any artery of the upper extremity, an adequate collateral circulation usually precludes the occurrence of gangrene. Gangrene has also occurred in cases in which there was no apparent evidence of embolism or thrombosis and it was attributed to spasm.[138]

Bronchopneumonia

The true incidence of this frequent complication of acute myocardial infarction is difficult to determine. On the one hand it is unrecognized when it complicates advanced pulmonary congestion associated with rales at the bases of the lungs; on the other hand it is often diagnosed clinically when the pulmonary signs and other clinical features are actually due to pulmonary embolism with infarction. Undoubtedly pulmonary congestion, pulmonary infarction and bronchopneumonia are often combined in the same person. Bronchopneumonia is commonly a terminal or terminating incident in fatal cases.

Rupture of the Heart

This is one of the commoner causes of sudden death in the first few weeks after acute myocardial infarction.[46, 57, 196, 129] Martland[103] found a rupture of the heart in 2 per cent of 2000 cases investigated by the medical examiner; these comprised about 7 per cent of the 318 cases of coronary occlusion in his series. While cardiac infarction due to coronary atherosclerosis and occlusion is by far the commonest cause of rupture of the heart, the latter may also result rarely from bacterial endocarditis, myocardial abscess due to sepsis, dissecting aneurysm of the sinus of Valsalva, gummatous (syphilitic) myocarditis, tuberculous perimyocarditis, echinococcus cyst and malignancy. Traumatic rupture of the heart is discussed in Chapter 44.

According to Fulton,[59] one eighth of the patients who succumb in the first three weeks after acute myocardial infarction die from rupture of the heart. The 44 cases of cardiac rupture reported by Nesvadba[114] represented 7 per cent of the fatal cases of myocardial infarction in his series. Krumbhaar and Crowell[85] found the cardiac rupture through the left ventricle in 225 cases and through the right in 32. The anterior surface was lacerated three times as often as the posterior surface. Infarction and rupture of the right atrium have also been reported (p. 516).

Rupture of the heart results from a through and through laceration of an infarcted area which is still soft and necrotic. The rupture occurs most frequently in the first week, sometimes in the second week, and rarely thereafter. In Fulton's series [illegible] death from cardiac rupture occurred within 17 days in all but one and the average was 9 days after cardiac infarction. It may occur in the first two or three days. Whereas softening of the myocardium is a major factor responsible for ventricular rupture, the height of the intraventricular pressure may also be important. Edmondson and Hoxie[46] found that patients who have hypertension which persists after infarction are three times more likely to develop cardiac rupture than those who have normal or subnormal blood pressures. Women are somewhat more susceptible than men. Although cardiac rupture may occur when the patient is in bed, occasionally a specific physical strain or continued normal activity after the myocardial infarction may contribute to the cardiac perforation. Thus while Friedman and White[57] encountered 10 cases of rupture of the heart (9.4 per cent) in 105 autopsied cases of myocardial infarction in a large general hospital, Jetter and White[74] found 16 instances of rupture of the heart (73 per cent) out of a total of 22 autopsied cases of acute myocardial infarction in mental institutions. The implication was that continued activity by mental patients with unrecognized myocardial infarction was an important factor in causing rupture of the heart. But although hypertension and exertion are accessory factors favoring cardiac rupture after myocardial infarction, cardiac rupture depends primarily on the site and extent of the infarct and is favored by absence of a collateral circulation and absence of fibrosis in the infarct.[196]

Rupture of the heart following cardiac infarction leads to hemopericardium, cardiac tamponade and sudden death. Occasionally the amount of blood in the pericardium may even exceed a liter, but usually about 250 cc is sufficient to cause cardiac tamponade. Death may occur within a few minutes after

the rupture but occasionally there is a survival period of a half hour or longer There has been at least a threefold rise in the prevalence of hemopericardium without rupture and a twofold increase of rupture of the myocardium in patients who received anticoagulant therapy during acute myocardial infarction in comparison with those who did not [15]

Rupture of the Interventricular Septum

Rupture of the interventricular septum after infarction of this portion of the myocardium is less common than that of the ventricular wall [65, 88] Edmondson and Hoxie[66] observed 13 instances of rupture of the interventricular septum compared with 56 of the left or right ventricle The perforation is usually a single one in the lower or central portion of the septum varying from pinpoint size to 6 cm in length occasionally there are two or three perforations

Unlike ventricular rupture rupture of the septum can be readily diagnosed antemortem [160, 110, 81, 101, 167] and may occasionally permit a period of survival of several months[114] or even up to five years [205, 16] Clinically the symptoms are those of severe myocardial infarction associated with intense dyspnea and increasing shock The symptoms and signs of right sided heart failure may develop rapidly The diagnostic feature is a loud and often roaring systolic murmur which is usually loudest in the fourth and fifth interspace near the left border of the sternum A systolic thrill is almost always present in the same region but it may be absent The prognosis is almost always extremely poor partly because the infarction in these cases is usually extensive and partly because of the added circulatory disturbance of the acute perforation itself In those who survive even for a few months there are usually symptoms and signs of left and right sided congestive failure

Rupture of a papillary muscle is a rare complication of cardiac infarction [183, 165, 1] It may be due also to bacterial endocarditis or trauma The posterior papillary muscle of the left ventricle is most often affected the anterior papillary muscle is next in frequency and rarely the papillary muscles of the right ventricle Sometimes there are no auscultatory findings but there may be a loud apical systolic murmur or a whistling to and fro murmur or a murmur and a thrill resembling those of a ruptured interventricular septum Pulmonary edema and progressive heart failure follow rapidly

Sudden Death

Sudden or unexpected death is a common termination of acute myocardial infarction It may be the only manifestation of the attack (p 513) or it may occur in any stage of the acute disease during convalescence Among its causes massive pulmonary embolism and rupture of the heart have already been mentioned It is believed that most often sudden death results from ventricular fibrillation or cardiac standstill although only rarely is it possible to demonstrate this electrocardiographically Of 16 instances of sudden death associated with coronary disease analyzed by Stroud and Feil [185] 8 were due to a sudden paroxysm of ventricular fibrillation and 8 to sudden ventricular standstill According to Brofman et al a difference in oxygenation of two adjacent areas of myocardium associated with a difference in electrical potential across the transitional zone acts as a trigger' to destroy the coordinated mechanism of the heart and thus induces ventricular fibrillation [24] In patients with complete heart block and Adams Stokes syndrome following cardiac infarction death may occur suddenly during a paroxysm of prolonged cardiac asystole It may follow the intravenous administration of various therapeutic agents such as aminophylline papaverine and quinidine A definite causal relationship between the drug and the fatality is usually difficult to establish since sudden death strikes so commonly in cases of acute myocardial infarction

Aneurysm of the Left Ventricle[184a]

Aneurysm of the left ventricle is usually due to myocardial infarction although rarely it may result from congenital defects trauma myocardial abscess and ulcerating bacterial endocarditis It is said to occur in 7 to 8 per cent of cases of cardiac infarction but it is probably much more frequent [15, 0, 151, 129] Applebaum and Nicolson[6] found ventricular aneurysm present in 57 (38 per cent) of 150 cases of coronary occlusive disease Inconspicuous aneurysms are easily overlooked at necropsy when the pouch is not distended with blood as it is during life

Following coronary occlusion the intraventricular tension stretches the noncontracting infarcted heart muscle and may a

produce a *localized bulge where the myocardium* consists only of a relatively weak thin layer of soft necrotic muscle and fibrous tissue *This bulge, known as a ventricular* aneurysm may not protrude beyond the remaining surface of the ventricle except during systole, or it may be so prominent that it resembles a tumor It may be filled with thrombus, the overlying pericardium is usually adherent Sometimes the aneurysm is partially calcified [139, 50] It may develop during the acute stage of infarction[99] and become



Fig 114 Left ventricular aneurysm due to old myocardial infarction Localized bulge above cardiac apex which showed diminished pulsations by fluoroscopy and kymography

more prominent after healing But often it is first recognized months or years after the acute infarction The wall of the aneurysm may be perforated but almost always during the acute phase only [illegible] The site of the aneurysm corresponds to the usual site of the infarcts at the apex and anterior wall of the left ventricle or at the base and posterior wall

Although there are no characteristic symptoms of ventricular aneurysm angina pectoris may be associated and symptoms of congestive heart failure are common Cerebral or other embolism may complicate endocardial thrombosis Physical examination may disclose a forceful and rather broad pulsation of the anterior chest wall at the level of the fifth rib or interspace just inside the midclavicular line *This pulsation is often distinguishable* from that of the apical impulse The heart sounds are frequently muffled and gallop rhythm is common

Roentgenologic examination[167] may disclose not only cardiac enlargement, but also a circumscribed bulge or hump in the lower left (ventricular) contour (Fig 114) or a sharp angulation or ledge which transforms this contour into oblong shape The aneurysm may be best visualized in the oblique positions Its shadow cannot be separated from the heart shadow in any position in which it is seen Occasionally its demarcation is accentuated when lime salts have been deposited in its wall [7] Fluoroscopic, roentgen kymographic, or electrokymographic[161] examination may reveal a paradoxical pulsation of the aneurysmal site, contrasting in direction with the pulsation of the remainder of the left ventricle but this may be observed also after myocardial infarction without distinct aneurysm

The electrocardiographic findings are those of old infarction of the anterior or posterior wall bundle branch block or non specific evidences of myocardial damage RS T segment elevations and cove plane inversion of the T wave ordinarily associated with acute myocardial infarction may be observed with ventricular aneurysm when cavity potentials are transmitted through a completely fibrotic aneurysmal wall[117] or may be due to potentials of the opposite hypertrophied wall [11] There may be widespread inversion of T waves in at least three precordial leads Goldberger and Schwartz[41] described electrocardiographic patterns of ventricular aneurysm in standard leads characterized by (1) small R_1 and deep S_2 and S_3 and (2) main deflection downward in the three standard leads due to unusual rotation of the heart A deep S may also be present in aV_F and a QS in lead aV_L and in one or more precordial leads

The diagnosis of ventricular aneurysm may be based on a history or definite electrocardiographic demonstration of previous myocardial infarction and the finding of a strong abnormal precordial pulsation contrasting with a weak first sound at the cardiac apex [87] The roentgenologic findings mentioned above may confirm this clinical diagnosis or suggest it independently A ventricular aneurysm must be differentiated roentgenologically from a tumor of the heart a local pericardial effusion pericardial cyst aneurysm of the sinus of Valsalva localized calcification of the pericardium gumma of the myocardium syphilitic aneurysm of the descending aorta and enlarged pulmonary conus

The outlook for patients with ventricular aneurysm is that of the underlying disease i e myocardial infarction Survival for ten years has been reported by Young and Schwedel [204] Death usually occurs from congestive heart failure recurrent myocardial infarction and peripheral emboli

Periarthritis of the Shoulder (Shoulder Hand Syndrome) and Other Skeletal Lesions

Pain stiffness and marked limitation of motion of the shoulder joint shoulder girdle and arm frequently result from acute myocardial infarction [3, 33, 5, 130] The symptomatology may vary from mild pain on motion with little or no limitation to severe pain with almost complete limitation of motion especially of abduction and external rotation (frozen shoulder)[164] Edeiken and Wolferth[63] reported 14 cases of persistent pain in the shoulder joint, usually developing coincidentally with or within four weeks after acute myocardial infarction In severe cases it may persist from six months to two years usually it subsides spontaneously but it may recur

Usually the left shoulder and arm are affected but the right side or both sides may be involved The predominance of the involvement of the left shoulder region suggests a causal relation to the distribution of the cardiac pain because in patients without a history of angina pectoris or coronary thrombosis periarthritis of the right shoulder greatly exceeds that of the left Furthermore there is a tendency for the right shoulder to be affected when the pain of myocardial infarction radiates to the right side [31]

This complication has usually been attributed to reflex spasm of the muscles and ligaments around the shoulder secondary to cardiac pain impulses which are referred to the same segments of the spinal cord as innervate the affected muscles and ligaments Boas and Levy[22] and Askey[5] suggested that these reflexes accentuated a previously existing but subclinical periarthritis Ernstene and Kinell[31] attribute the complicating syndrome to protective disuse of the shoulder and abnormal tension under pain of the muscles of the shoulder girdle and my own observations have led me to believe that disuse is at least an important contributory factor This explanation accounts satisfactorily for the tendency to involvement of the shoulder to which the pain is referred since this is the extremity which is favored and not used Furthermore periarthritis of the shoulder occurs very commonly independent of cardiac pain under a variety of circumstances which involve disuse and abnormal posture of the affected extremity

Meyer and Binswanger[131] observed pain stiffness swelling and disability of the joints of the right hand and wrist following acute myocardial infarction in 3 patients whose pain during the attack had radiated chiefly down the right upper extremity Prolonged disuse because of the pain was also invoked to account for this complication Askey[5] observed pain stiffness and swelling of the finger joints with glossy skin and purplish red discoloration in association with the shoulder pain In some cases there developed a thick

of the palmar aponeurosis resembling the early stage of Dupuytren's contracture[9] Because of the changes in the skin and the latter development Askey[8] concluded that the syndrome was the result of sympathetic nerve disturbance caused by myocardial ischemia and preexisting shoulder and hand lesions Trophic ulcers of the hand have been noted following myocardial infarction[169] Johnson[3] noted disabling changes in the hands resembling sclerodactylia in 39 (21 per cent) of a series of 178 consecutive cases of acute myocardial infarction He attributed these changes to anoxia of the tissues of the fingers caused by reflex vasoconstriction induced by cardiac pain But this explanation fails to account for the interval of three to sixteen weeks between the pain of the infarction and the development of the changes in the hands For Treatment see page 583

Mental changes, including agitation, reactive depressions and various psychoses, are more common than is generally recognized I am seeing an increasing number of patients whose persistent symptoms especially weakness and disability, are attributed to the damage of myocardial infarction, but who respond favorably to electroshock and related forms of therapy

Post Myocardial Infarction Syndrome

Dressler described a post-myocardial infarction syndrome in 20 patients[41a] The syndrome was characterized by protracted or recurrent fever, chest pain of the pleuropericardial type and a tendency to relapse A pericardial rub was heard frequently and roentgenograms suggested the presence of pericardial effusion in many of the cases The clinical picture was attributed to pericarditis, pleuritis and pneumonitis Excellent therapeutic results followed the administration of prednisone

INFARCTION OF THE ATRIA

Infarction of the atria due to coronary artery occlusion[200] ■ has until recently been noted rarely in comparison with the frequency of ventricular infarcts Bean[16] observed 2 atrial infarcts in a series of 287 cases of myocardial infarction and Feil et al[4] 2 others in 34 cases of myocardial infarction But Cushing and associates[24] observed 31 instances of atrial infarction (17 per cent) in a series of 182 cases of myocardial infarction In 6 of these the atrium alone was affected Slapak[174] reported 10 cases of atrial infarcts occurring as extensions of a ventricular infarct Atrial infarction is easily overlooked on gross examination of the heart, but its presence may be suggested by the finding of atrial mural thrombi which occur in 80 per cent of the cases[193] It is often difficult to find an occlusion of the corresponding artery supplying the affected area, but extensive and severe atherosclerosis or occlusion is usually present in the larger coronary arteries The right atrium (especially the appendage) is involved much more frequently than the left and usually on its anterior surface

Atrial infarction may result not only from coronary atherosclerosis but also from periarteritis nodosa, and from less specific obliterating endarteritis of the small branches of the coronary arteries It has also been noted in a case of an occluded congenital single coronary artery[150] and in cases of bacterial endocarditis with ulcerating lesions In some instances hemorrhagic necrosis of the atrial wall resembling an infarct results from the perforation of a true or false aneurysm

Rupture of the atrial wall may result from infarction Of 710 cases of rupture of the heart collected by Krumbhaar and Crowell[85] and by Davenport[34] 7 per cent involved the atria Of 55 cases of atrial rupture collected by Clowe, Kellert and Gorham,[30] 39 were situated in the right atrium, 15 in the left, and 2 in the interatrial septum Clowe et al called attention to the high incidence of atrial rupture (47 7 per cent) before the age of 40 as compared to 6 7 per cent for ventricular rupture during this age period The rupture of the atrium usually extends into the pericardium, producing hemopericardium, but occasionally it extends into the pleural cavity

No distinctive clinical picture has yet been evolved for atrial infarction In some of the cases reported the symptoms and signs were indistinguishable from those due to ventricular myocardial infarction In many instances, atrial infarction is combined with ventricular infarction and the clinical picture is that of the latter Symptoms may first appear with rupture of the atria and may consist of shock and rapid death due to cardiac tamponade

Recent interest in infarction of the cardiac atria has centered in efforts to associate this condition with a distinctive electrocardio-

graphic picture Abramson et al[1] noted elevation of the P Q segment in lead I on cauterization of the left atrium of dogs and cats and depression of this segment on cauterization of either surface of the right atrium Depressions of the P T segments in leads II and III occur with similar injury to either atria Langendorf[20] first described a case of infarction of the right atrium in which characteristic electrocardiographic changes were noted Young and Koenig[69] described deviations of the P Q segment in 3 of their 4 cases of atrial infarction However Cushing et al[34] noted such P Q abnormalities infrequently in their 31 cases In the case of atrial infarction reported by Hellerstein[65] the diagnosis was made ante mortem on the basis of changing atrial mechanism heart block and elevation of P T_A segment in leads II and III (posterior wall atrial infarct) I saw a patient who experienced the clinical features of acute myocardial infarction but the electrocardiogram showed minimal abnormalities except for nodal bradycardia Postmortem examination showed thrombosis of the ostium of the right coronary artery with extensive infarction of the right atrium with less involvement of the posterior wall of the left and right ventricles

The *diagnosis of atrial infarction* in cases of clinical myocardial infarction may be suggested by (1) atrial arrhythmias especially if they change rapidly including atrial fibrillation or flutter atrial premature beats nodal rhythm sinus arrest (2) elevation or depression of P T_A segment especially depression since most of the infarcts are anterior (3) changing contour of the atrial T wave (T_A) (4) changing contour of the P waves (5) atrioventricular block[180 63]

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Chapter 21

ACUTE CORONARY OCCLUSION AND MYOCARDIAL INFARCTION

Diagnosis, Differential Diagnosis, Prognosis, and Treatment

DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

In most cases of acute myocardial infarction the diagnosis is relatively simple and may be ventured with reasonable certainty on the basis of the history and symptomatology alone. Missed diagnoses are due to (1) inadequate care in taking the history, (2) multiple attacks of chest pain within a short period of time without a clean cut sharp onset, (3) no chest pain or relatively mild pain overshadowed by pulmonary edema, paroxysmal dyspnea, weakness or shock, (4) no prolonged attack of pain at rest but angina pectoris on effort, usually more frequent and with less provocation, and often associated with fever which is overlooked. Under all these circumstances error will be avoided if the diagnosis of myocardial infarction is considered and serial electrocardiograms taken.

Chest Pain Suggesting Cardiac Infarction

Severe oppressive pain over the lower sternum or more extensively over the precordium or anterior chest lasting at least a half hour and not relieved by rest or nitrites is sufficient to warrant a tentative diagnosis of acute myocardial infarction in the absence of some other obvious cause of the pain. Characteristic radiation of the pain to the neck, shoulders or arms confirms the likely origin of the pain in the heart.

A rapid fall of blood pressure within 24 hours or even a more gradual fall in the next few days is an important confirmatory sign. A moderate elevation of temperature and leukocytosis, an accelerated rate of sedimentation of erythrocytes and an increase in serum transaminase (p. 519) are additional features supporting the diagnosis. If the pain is classic in its character, location, radiation, severity and duration, the diagnosis of *acute coronary occlusion* is proper regardless of electrocardiographic changes. If the pain is classic but the electrocardiogram is not distinctly that of acute myocardial infarction and there is no fever, an acute coronary occlusion without myocardial infarction should be considered. Classic chest pain with fever, leukocytosis, etc., justifies the diagnosis of acute myocardial infarction even without distinctive electrocardiographic changes, but one must be cautious to exclude other causes of chest pain. In general, the more definite and complete the clinical picture, the less the need for characteristic electrocardiographic changes to establish the diagnosis. But if the clinical picture is at all atypical or in any way uncertain, the diagnosis can only be certified by the presence of unequivocal electrocardiographic changes.

Shock, Syncope or Prostration Suggesting Acute Cardiac Infarction

Shock, prostration or syncope occasionally dominates the picture of acute myocardial infarction, but a careful history and clinical observation may disclose the presence of chest pain and other manifestations. A definite diagnosis, however, depends on the distinctive electrocardiographic changes.

Acute Pulmonary Edema Suggesting Acute Cardiac Infarction

Acute pulmonary edema without obvious cause should suggest the possibility of acute myocardial infarction, but electrocardiographic confirmation is necessary for a definite diagnosis.

Development or Intensification of Heart Failure Suggesting Acute Cardiac Infarction

When a person begins to experience attacks of nocturnal dyspnea or dyspnea on the mildest exertion or when a patient with such symptoms suddenly presents enlargement of the liver engorgement of the peripheral veins or peripheral edema the possibility of a recent cardiac infarction should be investigated The diagnosis then depends essentially on the exposition of characteristic electrocardiographic changes The electrocardiogram in this type of case having often been altered by a previous infarct the fresh infarction may be documented only by changes in the QRS or T waves without the distinctive pattern of a primary acute cardiac infarct

Other Symptoms Suggesting Acute Cardiac Infarction

The sudden and unexplained development of extreme fatigability or weakness attacks of dizziness or syncope indigestion brief episodes of dyspnea and pallor or cyanosis, palpitation and a cardiac arrhythmia, or the occurrence of systemic embolization may each prove to have been due to an acute myocardial infarction Frequent electrocardiographic examination is the only method of minimizing diagnostic oversight in this type of case Special attention is directed to the relative frequency with which cerebral vascular accidents are due to or associated with acute myocardial infarction and the necessity of routine electrocardiography to discover this association (p 541) Similarly unexplained postoperative fever shock or symptoms of cardiac failure often interpreted as direct complications of a surgical procedure may be found on electrocardiographic examination to be caused by cardiac infarction The diagnostic value of routine preoperative electrocardiograms for control purposes appears obvious

Electrocardiographic Diagnosis of Acute Cardiac Infarction

The electrocardiographic changes associated with acute myocardial infarction have been discussed in detail in a previous section to which the reader is referred (p 521) Although the diagnosis of acute myocardial infarction should be based on an appraisal of all the laboratory and clinical features as well as the electrocardiogram, certain electrocardiographic findings in themselves justify the diagnosis In the absence of the classic clinical symptoms and signs of acute myocardial infarction the relation of certain mild or nonspecific symptoms to cardiac infarction is sometimes betrayed only by electrocardiographic study However, occasionally the conventional 12 lead electrocardiogram may not show changes suggestive of myocardial infarction despite typical clinical features Sometimes, as in infarction of the posterobasal wall (high posterior wall) of the left ventricle, the spatial vectorcardiogram may indicate myocardial infarction when the conventional electrocardiogram is virtually normal (p 538)

Electrocardiographic Differential Diagnosis

Discordant RS T elevations and depressions in leads I and III may be encountered in conditions causing advanced *left or right ventricular hypertrophy* and *left or right bundle branch block* but in these cases the RS T segment is usually elevated and concave upward in the lead in which T is upright and depressed in the lead in which T is inverted Other features of the electrocardiogram of bundle branch block (p 396) also help to distinguish it from that of acute myocardial infarction The frequency with which bundle branch block conceals the electrocardiographic changes of acute myocardial infarction and the circumstances under which the latter may be recognized electrocardiographically when bundle branch block is present have been discussed (p 533) In the precordial leads Q waves and elevation or depression of the RS T segment may be due occasionally to left or right ventricular hypertrophy or dilatation [94]

Acute pericarditis like acute myocardial infarction may be documented in its early stages by RS T elevations But the RS T segment elevations in acute pericarditis are concordant i e they occur simultaneously in leads I and III (and usually also in lead II) (p 597), whereas those in myocardial infarction are discordant, i e, an elevated RS T in lead I is associated with a depression in lead III and vice versa The RS T elevation in acute pericarditis like that in acute myocardial infarction, may appear only in lead I or leads I and II, while the RS-T segment in lead III is isoelectric A distinction may still be made by the fact that the elevated RS T segment in acute pericarditis is either concave upward or horizontal to the crest of the T

wave whereas it is usually convex upward in cases of acute myocardial infarction The Q waves seen in lead I and in the precordial lead after anterior wall infarction or in leads II and III with posterior wall infarction do not occur with acute pericarditis alone

Electrocardiographic differentiation may be especially difficult when cardiac infarction is complicated by acute pericarditis as it is in at least 20 per cent of cases The combination of infarction with pericarditis is suggested by the presence of concordant ST elevations as in isolated acute pericarditis, in association with Q waves in lead I aVL and the precordial leads or in leads II and III and aVF The combination may also be revealed by transient concordant RST elevations as in pericarditis with subsequent discordant elevations and depressions in leads I and III as in myocardial infarction

Massive pulmonary embolism (acute cor pulmonale) may produce electrocardiographic changes suggestive of posterior wall infarction (p 961) Usually the electrocardiographic pattern of massive pulmonary embolism may be differentiated by the presence of a prominent S_1 a tendency to right axis deviation a low origin of the T wave in leads I and II with a staircase ascent of ST_1 or $_2$ and frequent inversion of the T wave in the precordial leads abnormalities not seen with posterior wall infarction Furthermore the T wave inversions in leads II and III appear within 12 hours after the onset whereas those associated with posterior wall infarction appear considerably later

Digitalis may produce electrocardiographic changes which may obscure those of acute myocardial infarction If the latter diagnosis is suspected but uncertain electrocardiograms should be made if possible before administering digitalis Usually digitalis causes a depression of the RS T segment and inversion of the T wave in all leads These changes should not be confused with those of acute myocardial infarction but they may modify and obscure the characteristic RS T segment elevations and T wave inversions associated with the latter Occasionally digitalis produces electrocardiographic changes which may be confused with those of posterior wall infarction namely an RS T elevation in lead III and an RS-T depression in lead I (and lead II) in electrocardiograms which previously showed left axis deviation A differentiation can usually be made by the presence of Q waves in leads II and III in cases of posterior wall infarction and by the upward convexity of the elevated R T segment in the former as contrasted with the upward concavity of the elevated R T segment due to digitalis The Q T interval is frequently shortened by digitalis and lengthened after acute cardiac infarction but this is not a dependable distinction

A *transverse position* of the heart may be associated with a large Q and inversion of the T wave in lead III These findings may be misinterpreted as indicating a posterior wall infarction if the electrocardiogram was made because of non specific abdominal or chest discomfort The Q_3 often present with myocardial infarction does not appear as a result of the transposition alone The Q_3 wave due to position may disappear and the T wave become upright in an electrocardiogram taken with the patient upright and the lungs in deep inspiration By the analysis of unipolar limb leads the Q and T changes may be revealed as the effect of the position of the heart and not of myocardial infarction When Q_3 is due to posterior wall infarction aVF the augmented unipolar left foot lead almost always presents a Q wave which is 25 per cent or more of the R wave when the Q_3 wave is due to transverse or semi transverse position of the heart a significant Q wave usually does not appear in aVF [95, 110] Esophageal leads at the ventricular level also reveal characteristic Q wave changes in the cases due to posterior infarction ■ In themselves Q_3-T_3 changes are insufficient for a diagnosis of posterior wall infarction unless fortified by the characteristic RST elevation and subsequent serial changes or by the clinical history and findings

Acute pancreatitis is associated occasionally with RS-T segment and T wave changes which may simulate those of acute myocardial infarction

DIFFERENTIAL DIAGNOSIS

Formerly any consideration of the differential diagnosis of acute myocardial infarction was apt to emphasize the frequency with which this condition was overlooked and mistaken for a variety of other conditions In recent years increased knowledge of the features of acute myocardial infarction a general awareness of its common occurrence and the widespread use of the electrocardiograph

often with exaggerated interpretations of minor or non specific changes have led to the opposite tendency of erroneously diagnosing numerous other conditions as instances of acute myocardial infarction In differentiating between cardiac infarction and the following diseases the physician must be alert to the possibility of error in either direction

ANGINA PECTORIS

The pain of acute myocardial infarction is distinguished from that of angina pectoris by its longer duration (more than 30 minutes and usually for hours) its persistence with the patient at rest if it began during exertion, its failure to respond to nitroglycerin (but trial of this drug is rarely necessary for the differentiation) It is also distinguished by its frequent association with dyspnea or other evidences of heart failure a fall in blood pressure and other evidences of shock and by the development of fever and leukocytosis and an increased sedimentation rate When pain is the only symptom of acute myocardial infarction especially when the pain is relatively mild and not very prolonged it may be difficult to distinguish cardiac infarction from angina pectoris In such instances definite differentiation can be made only by repeated examinations of electrocardiograms temperature blood count and sedimentation rate It should be reemphasized that paroxysms of angina pectoris which occur at rest after having previously occurred only on effort or suddenly increase in severity and frequency may actually represent attacks of myocardial infarction to be discovered only by objective clinical laboratory and electrocardiographic examination

As a rule the electrocardiogram is normal in patients who have recently suffered chest pain due to angina pectoris and there is no difficulty in differentiating it from acute myocardial infarction Electrocardiograms taken *during an attack of angina pectoris* may disclose concordant RS T depressions and occasional T wave inversions in the standard and in the precordial leads which, however, are transient (p 449) Wilson and Johnston[142] have noted in 5 cases of angina pectoris electrocardiographic changes similar in character and magnitude to those produced by myocardial infarction As a rule there were deep S waves and pronounced ST depressions in leads II and III with occasional T wave inversion during the attack of spontaneous or induced pain But these changes disappeared rapidly In one there was discordant RS T elevation in leads II and III with depression in lead I transiently during the pain When such changes persist after subsidence of the pain or progress through the stages described for acute myocardial infarction, one should question the diagnosis of angina pectoris When a patient happens to experience a transient attack of anginal pain during the recording of an electrocardiogram the interpretation of conspicuous electrocardiographic abnormalities should be deferred until another record is taken an hour or more after the pain subsides Since many patients with angina pectoris have suffered previous myocardial infarcts their electrocardiograms may disclose evidences of intraventricular conduction defects and Q and T wave changes due to the old infarcts

Acute Coronary Insufficiency

So-called coronary insufficiency, an ill defined term of varied and inconsistent usage (p 461) presents a problem in differential diagnosis under the following circumstances

1 Sometimes cardiac pain is intermediate in duration and severity between that usually associated with angina pectoris and that of acute myocardial infarction If there is no fever, leukocytosis and increased sedimentation rate, and no characteristic electrocardiographic signs of transmural myocardial infarction, acute myocardial infarction cannot be diagnosed The condition is one of *prolonged angina pectoris* probably due to an acute coronary occlusion without infarction or *to some determinable factor which diminished* coronary blood flow or increa ed the work of the heart

2 Sometimes the clinical history of pain suggests either angina pectoris or myocardial infarction and the electrocardiogram discloses persistent ST segment depressions and/or T wave inversions In such cases the basic pathologic change is revealed by other clinical findings Fever leukocytosis rapid sedimentation rate shock, pulmonary edema and rales at the bases of the lungs indicate that the pain represents myocardial infarction The electrocardiographic ST-T changes then merely localize the infarction to the subendocardium the absence of Q waves and discordant ST elevations and depressions denote absence of through and through (transmural)

infarction. Or the classic electrocardiographic changes of a new transmural infarct may be modified or obscured if there was a previous myocardial infarct or if there is considerable left ventricular hypertrophy. If fever, leukocytosis, and other signs are absent, then the diagnosis should be angina pectoris. The persistent ST depressions or T wave changes may then denote cardiac hypertrophy, old myocardial infarction, digitalis effect or subendocardial ischemia without infarction. In the latter circumstance the cause for *persistence* of the ischemia may be acute anemia, pulmonary embolism, shock, aortic stenosis or paroxysmal tachycardia, but most often it is due to an acute coronary occlusion without myocardial infarction. Transmural infarction, subendocardial infarction, coronary occlusion without infarction, subendocardial ischemia and angina pectoris are all consequences of coronary insufficiency; it is important to attempt to define the underlying pathology.

DISEASES OF THE CHEST

Pulmonary Embolism

When manifested by chest pain of a pleuritic type or hemoptysis, pulmonary embolism is easily diagnosed, but hemoptysis is usually absent and the pain may resemble that of myocardial infarction. Then the differentiation depends on the presence or absence of the characteristic electrocardiographic changes associated with myocardial infarction.

Cardiac Arrhythmias

The sudden advent of an arrhythmia, especially when associated with tachycardia, is sometimes attended by oppressive substernal pain which may be prolonged, and by palpitation, angor animi, cold sweat and occasionally by dyspnea and other evidences of heart failure. Such a picture is often mistaken for acute myocardial infarction. Discovery of the arrhythmia either by clinical or electrocardiographic examination does not always exclude an acute myocardial infarct, since the latter may be associated with certain arrhythmias at its onset. Cessation of the pain and other symptoms when the arrhythmia disappears and absence of the characteristic electrocardiographic changes of cardiac infarction in subsequent records exclude this condition. However, electrocardiographic changes resembling those of posterior myocardial infarction have been noted after cessation of a paroxysmal atrial tachycardia.[49, 40]

Occasionally acute myocardial infarction is associated with the electrocardiographic changes of the W P W syndrome.[15] Since the electrocardiographic changes of myocardial infarction may be obscured in the presence of a W P W pattern,[illegible] it has been suggested that the former will become more apparent if a normal conduction mechanism is first restored by the administration of quinidine.[181]

Acute Pericarditis

The combination of chest pain, fever and a pericardial rub may present difficulty in distinguishing between an acute pericarditis and acute myocardial infarction associated with pericardial involvement.[144] The differential diagnosis depends on serial electrocardiograms which sooner or later usually disclose the changes of myocardial infarction if the latter is the basic disease. Pericarditis independent of myocardial infarction may be suspected if there is another underlying causative disease such as rheumatic fever, tuberculosis, or neoplasm. Certain forms of benign idiopathic pericarditis (p. 603) occurring in young persons are often accompanied only by fever, mild pain and a considerable pericardial effusion, which is unusual in cases of cardiac infarction. However, in many such cases myocardial infarction (p. 603) had been diagnosed or considered. The electrocardiographic distinction has been discussed (p. 552).

Spontaneous Pneumothorax

This is distinguished by absence of the electrocardiographic changes of myocardial infarction and by distinctive physical signs and roentgen ray findings in the lungs.

Dissecting (Nonsyphilitic) Aneurysm of the Aorta[33, 77]

Like cardiac infarction, dissecting [illegible] aneurysm occurs predominantly among [illegible] between the ages of 40 and 70 with [illegible] hypertension. However, dis[illegible] aorta is not as uncommon [illegible] adults as was formerly beli[illegible] association with pregnancy [illegible] tion of the aorta. In young [illegible] tacular dissecting aneurysm [illegible] occur in the absence of h[illegible] there is an associated co[illegible]

Weakness of the med[illegible] disease is the basic d[illegible]

ture of branches of the vasa vasorum causes a tear through the intimal surface and permits subsequent dissection of the main aortic blood stream along the outer layers of the diseased media. The rupture and dissection may be favored by pronounced hypertension which may have mounted suddenly because of physical effort or emotional strain. But this relationship may only be a coincidence. The intimal tear occurs commonly a few centimeters above the aortic valve or near the origin of the left subclavian artery, but it may occur anywhere in the thoracic aorta and there may be multiple tears. When there is a transverse laceration across the commissures, the latter may slip down and the aortic cusps may not approximate, with consequent aortic insufficiency.[78] The tear may heal without rupture of the aorta or dissecting aneurysm and the patient may succumb eventually from congestive heart failure due to aortic insufficiency. Dissection through the pericardial wedge may cause pericarditis and a pericardial rub may be heard before the final blowout. Or else the blood may dissect its way throughout the thoracic and abdominal aorta involving various large branches such as the coronary, the innominate, carotid, subclavian, intercostal or iliac arteries. One or more of these vessels may be partially or completely occluded by blood clot. Transient strokes, other cerebral focal manifestations and differences in blood pressure and pulses in the two sides of the body may be noted.

Death usually occurs suddenly, after a relatively quiescent stage of a few hours or days, but sometimes only after months or years. According to Mote and Carr[90] dissecting aneurysm of the aorta is responsible for 1 per cent of non traumatic sudden deaths in coroners' statistics. Death is due usually to a perforation of the aneurysm through the adventitia into the pericardium with subsequent hemopericardium and cardiac tamponade. But the aneurysm may also perforate into the left pleural cavity or more rarely into the mediastinum, right pleural cavity or pulmonary artery, or into the abdominal cavity by way of the retroperitoneal tissues. Occasionally recovery is possible when the dissection leads back through a second intimal perforation into the original aortic lumen, producing the so-called double-barrelled aorta.[107] But even this healed channel is subject to subsequent rupture.[104]

Although many of the symptoms of dissecting aortic aneurysm resemble those of acute myocardial infarction, a careful history of the onset and development of symptoms, especially of the character, location and radiation of the pain, and detailed examination usually permit a distinction.[47] Persistence of hypertension even when there is evidence of shock is more likely to occur with dissecting aneurysm than with myocardial infarction. A difference in blood pressure in the two arms favors dissecting aneurysm. Repeated examinations often reveal changes in pulses. In both conditions there is severe retrosternal or precordial pain, but the pain of dissecting aortic aneurysm usually occurs more suddenly, is often of an immediate tearing quality and is apt to have more widespread radiation to the back of the head and neck, the posterior thorax, the lumbar region, the epigastrium or the lower extremities. Dizziness or syncope, nausea and vomiting, dyspnea and cold clammy extremities are common to both, but with dissecting aortic aneurysm, temporary loss of vision, numbness in one or both legs or arms, paralysis of an extremity, or transient changes in reflexes and hematuria are much more common at the outset. Dysphagia due to pressure of the false sac on the esophagus occurs rarely; when present, however, it is a distinguishing diagnostic feature, for it is not encountered with acute myocardial infarction.

There may be signs of aortic insufficiency not previously present, or of a left pleural effusion. Pulsations may be absent in branches of the subclavian or iliac artery. There may be bizarre neurologic changes in the legs due to circulatory deficiency of the cord caused by rupture into the intercostal or lumbar arteries.[135] Because of the absorption of old blood the icterus index may be elevated, the elevation sometimes persisting for two weeks if the patient survives that long. Pronounced anemia may occur and its presence favors a diagnosis of dissecting aneurysm rather than myocardial infarction.

Roentgenologic examination sometimes discloses a distinctive progressive widening of the aorta, which may appear irregular and distorted by shadows along its branches. Aortic pulsations are diminished.[116] Successive films may show distinctive evidence of extension of the dissection. Angiocardiography may reveal constriction of the aortic lumen.[11]

Absence of the typical electrocardiographic changes of acute cardiac infarction is a critical differential diagnostic feature, but there may be non specific RS T and T wave alterations Occasionally a dissecting aortic aneurysm may produce myocardial infarction by extending along a major coronary artery and thus forming a hematoma, the pressure of which occludes the lumen [100]

Spontaneous Interstitial Emphysema of the Lung (Mediastinal Emphysema)[45]

Hamman[44] called attention to the spontaneous occurrence of mediastinal emphysema without antecedent trauma in apparently healthy individuals and to the possibility of its confusion with acute myocardial infarction Occasionally spontaneous interstitial emphysema and myocardial infarction are associated [illegible] Spontaneous mediastinal emphysema may be characterized by an abrupt onset of severe chest pain in the substernal region radiating to the neck and left arm The true cause of the pain may be betrayed by the pathognomonic sign of very loud peculiar crunching crackling or bubbling sounds over the sternum and precordium synchronous with cardiac systole and occasionally also with diastole Roentgenograms of the chest may also reveal shadows of air in the mediastinum itself [45] There may be T wave changes in the electrocardiogram but not the characteristic changes of myocardial infarction In one reported case mediastinal emphysema complicated myocardial infarction [54]

According to Macklin[79] interstitial emphysema of the lung results from increased intra alveolar tension which forces air from the alveoli into the adjacent vascular sheaths along which the air dissects its way to the mediastinum It is important not to mistake mediastinal emphysema for acute myocardial infarction since the former condition runs a benign course with complete recovery in several days Occasionally however it may recur

Many *other diseases of the thoracic organs or chest wall* may on occasion simulate or be simulated by acute cardiac infarction These include syphilitic aortitis with aortic aneurysm pneumonia pleurisy, massive collapse of the lung carcinoma of the lung diaphragmatic or paraesophageal hernia herpes zoster costochondral arthritis rupture of the costochrondral junction and diseases of the spine or shoulder with referred pain to the anterior chest An awareness of these possibilities and a careful regard for the previous history development of symptoms and systematic examination including electrocardiography and roentgen examination of the chest will almost always permit a differentiation In instances of malignant neoplasms of the lung mediastinum or esophagus invasion of the pericardium and heart wall may occur resulting not only in chest pain but in electrocardiographic changes such as RS T elevations as in the case reported by Rosenbaum et al [108]

Attention should be called also to malingerers familiar with the symptoms of cardiac infarction whose complaints are designed to obtain disability insurance payments injections of opiates if they are addicts or other benefits Such dissemblers may even take digitalis to produce electrocardiographic changes which however are usually distinctive of that drug (p 209)

ABDOMINAL CONDITIONS RESEMBLING CARDIAC INFARCTION

Acute Indigestion

The error of diagnosing acute cardiac infarction as acute indigestion is becoming less common On the other hand I have observed a growing tendency to err in the opposite direction by labeling many episodes of indigestion as myocardial infarction A definite diagnosis of cardiac infarction should be made only if the clinical features the electrocardiographic changes or both are sufficiently characteristic

Acute Surgical Abdominal Disease

Radiation or predominance of the pain of myocardial infarction over the upper abdomen accompanied by evidence of shock may compose a clinical picture resembling an acute surgical condition of the abdomen [71] such as a perforated peptic ulcer cholelithiasis and acute cholecystitis acute pancreatitis acute intestinal obstruction or even acute appendicitis Conversely sometimes one of these conditions as well as an attack of renal or ureteral colic with reflex ileus and pain in the abdomen or chest biliary colic sigmoid spasm food poisoning a tabetic crisis or other abdominal disease may be mistaken for cardiac infarction Further ambiguity is contributed by the electrocardiographic changes which sometimes accompany

a perforated peptic ulcer, acute pancreatitis[52] and acute postoperative peritonitis.[5] However, these changes should rarely be confused with those characteristic of acute myocardial infarction. Careful study of the past and present illnesses will usually result in a proper differentiation.

Among other conditions reported as occasionally simulating cardiac infarction are diabetic coma, sickle cell anemia during a hemolytic crisis[131] and Addison's disease during a crisis.[113] Although electrocardiographic changes may occur in these conditions, they do not closely approximate the characteristic patterns associated with cardiac infarction (p. 521).

PROGNOSIS

MORTALITY RATE OF THE ACUTE ATTACK

The outcome of an attack of acute cardiac infarction is unpredictable, on the one hand because of the constant threat of sudden unexpected death even for persons convalescing favorably, and on the other hand because of the possibility of long survival even for persons apparently critically ill. The mortality rate from the acute attack of myocardial infarction (i.e., within four to six weeks after onset) has been reported by many observers as averaging about 30 to 50 per cent. However, Bland and White[15] reported an immediate mortality (first four weeks) of 19 per cent in 200 cases of coronary thrombosis (many of whom had already survived the critical period when first seen in consultation), and Master, Jaffe and Dack[84] reported a mortality rate of 16.5 per cent in 267 attacks. Among patients apparently suffering their first attack of acute coronary thrombosis these observers noted a mortality rate of only 8 per cent.

It is probable that as milder cases are identified, the mortality rate from first attacks of acute myocardial infarction, excluding those in which death struck before a physician was consulted, will not exceed 10 per cent. Many mild cases treated at home by the family physician are not included in the statistics reported from large hospitals or by cardiac specialists who are apt to see the most severe cases. Studies in which "mild" cases are segregated from severe ones on the basis of various early clinical features (p. 573) indicate that the mortality rate in the former group is less than 5 per cent.[6, 112] Autopsy findings indicate that death occurs in a great majority of instances after multiple coronary occlusions, thus, not only is survival the rule after the first occlusion but this attack is often unrecognizable or unrecognized clinically.

Most deaths from acute myocardial infarction occur within the first week and a large percentage within the first 48 hours. In a study of 342 cases of acute myocardial infarction by Ball et al.,[7] there was a mortality within 24 hours of 1 per cent from sudden death with shock and of 5 per cent from ventricular fibrillation. Another 7 per cent of the patients died of delayed ventricular fibrillation, and 6 per cent of heart failure or shock within the first week. An additional 5 per cent died of ventricular fibrillation and 2 per cent from congestive heart failure during the first month. Thus there was a total mortality of 26 per cent in one month. This study excluded 55 episodes of acute myocardial infarction which terminated fatally with associated clinical or autopsy evidence of thrombosis or embolism in vessels other than the coronary.

With allowance for the possibility of sudden unexpected death at any time, the outlook for survival of the acute attack improves as the first week elapses without complications. The second week remains a critical period with danger of sudden death from pulmonary embolism, ventricular fibrillation, cardiac standstill or cardiac rupture, or of more gradual death from congestive heart failure, bronchopneumonia, progressive myocardial infarction or peripheral emboli. After the second week recovery from the acute attack is probable if there is no fever, little or no evidence of heart failure and no other gross complications persisting from the earlier stages.

FACTORS INFLUENCING PROGNOSIS

Age

Most observers have found the mortality to increase with the age of the patient. Woods and Barnes[147] noted that the mortality was twice as great beyond the age of 60 as below. However, I have been impressed by the relatively high percentage of patients who died of their first attack of myocardial infarction below the age of 40. In most of these there was a bad family history of frequent coronary disease. But young persons who recover from

the acute attack survive much longer than older recovered patients, and are more likely to be free from evidence of congestive heart failure and angina pectoris

Previous Attacks of Myocardial Infarction

The mortality rate is significantly higher in patients presenting a history or evidence of previous attacks of acute myocardial infarction[147] This applies particularly to those patients who suffer from chronic heart failure as a result of the previous attack or whose fresh attack was characterized by the initiation or intensification of congestive heart failure

Severity and Duration of Pain

When *severe pain* persists for more than 24 hours when it appears intractable and is incompletely alleviated by opiates the outlook for survival is usually unfavorable

Shock

When myocardial infarction is accompanied by an extreme degree of shock or when evidence of shock persists after several days the outlook is unfavorable That the mortality has been found relatively high (80 to 90 per cent) in patients whose blood pressure falls to 80 mm Hg or less or whose pulse pressure is 20 mm or less expresses the same fact since these merely attest to the severity of shock Occasionally this extravagant drop in blood pressure is followed by a considerable rise after a few hours and the patient subsequently recovers

Heart Failure

Since heart failure is one of the chief causes of death during the acute attack the development of acute pulmonary edema or of other symptoms of left or right-sided heart failure is inauspicious Yet it should not necessarily be viewed ominously unless the pulmonary edema persists more than 24 hours Some evidence of left ventricular failure occurs frequently at the very onset of acute myocardial infarction and is not significant for prognosis A heart rate of 110 or higher persisting during the first week of the attack usually is associated with heart failure with or without shock and has been found to be an unfavorable prognostic sign

Fever and Leukocytosis

In general temperatures of 104 or higher or a white blood count above 20 000 denotes extensive or progressive myocardial infarction or a serious complication and is associated with a high incidence of mortality[1 2] A similar significance is attached to the persistence of even moderate fever and leukocytosis for more than one week after the onset of the attack

Diabetes

The mortality from acute myocardial infarction is strikingly higher among diabetic than among non-diabetic patients[20] The late survival rate following myocardial infarction is substantially lower among diabetics since less than 20 per cent lived five years and only 3 6 per cent for ten years

Electrocardiographic Changes

Although it was formerly thought that a typical electrocardiographic pattern of anterior wall infarction augured a somewhat higher mortality rate than that of infarction of the posterior wall it now appears that the location of the infarct has not in itself prognostic significance[147] But my clinical impression persists that posterior wall infarction is usually associated with a less stormy course and a more favorable outlook than infarction of the anterior wall of the left ventricle When the electrocardiographic changes are not clearly those of either anterior or posterior wall infarction the mortality rate seems to be higher[147 23] perhaps because the indefinite electrocardiographic patterns usually denote multiple cardiac infarcts

Cardiac Arrhythmias

The mortality rate is probably significantly increased when atrial fibrillation or flutter ventricular tachycardia or signs of intraventricular block are present However Edeiken[44] recorded recovery from acute myocardial infarction of a patient with a ventricular rate exceeding 300 According to Askey and Neurath[4] cardiac infarction is associated with a higher mortality when atrial fibrillation is present than in its absence but the mortality rate is strikingly increased only if the fibrillation persists A very high mortality rate is associated with the development of complete heart block especially when symptoms of the Adams-Stokes syndrome appear Premature beats occurring infrequently are of no significance But Woods and Barnes[147] noted that among patients with one or more premature ventricular beats in every ten normal beats 14 of 17 died whereas all of the group with one premature beat in twenty or more survived

Embolization

The occurrence of pulmonary, cerebral visceral or peripheral embolism is associated with a high mortality

PROGNOSIS AFTER RECOVERY FROM THE ACUTE ATTACK

Following recovery from the acute attack, the patient's outlook is much more favorable than was formerly recognized. At least 40 per cent of the patients survive for more than ten years and at least 70 per cent for five years or longer. Of Bland and White's[15] 162 patients who recovered from the immediate attack, 31 per cent survived for ten years or longer, and 18 per cent were alive at their last follow up. The younger the patient at the onset, the longer was the period of survival. In a study of 100 consecutive patients with coronary thrombosis followed since 1930, Smith[115] found that there were 66 survivors after ten years, and 16 known survivors at the end of twenty years. Sixty nine were known to be dead and 15 lost to follow up at the end of twenty years. However, 25 per cent died within the first year after the myocardial infarction, indicating a relatively favorable outlook with survival beyond that time. Similarly, Cole et al.[8] reported that 43.9 per cent of 285 patients survived for more than ten years and one-tenth for more than fifteen years after their initial attack of myocardial infarction. Among 211 patients who lived more than two months after a first attack of acute myocardial infarction, Weiss found that 77 or 36.5 per cent survived for more than ten years.[140] Recently, Drake[35] reported a proven case of cardiac infarction in which the patient survived for forty years after the first attack at the age of 40. These statistics are presented not to minimize the seriousness of acute myocardial infarction, but to mitigate in part the excessive pessimism it inspires. The thought of possible long and useful survival is particularly sustaining to patients who associate "heart attack" only with sudden death, limited duration of life and invalidism.

RESIDUAL SYMPTOMS AND REHABILITATION AFTER ACUTE CARDIAC INFARCTION

Unfortunately, in many cases recovery from the acute attack is followed by distressing symptoms, restricted activity or invalidism. Palmer[10] found that of 212 patients who had survived three months or longer after coronary thrombosis, about one fourth were able to lead fairly active lives. Similarly, Bland and White,[1] in a study of 162 private patients who survived the acute attack, noted that about one third could pursue a fairly active life with little or no restriction because of cardiac symptoms. Bland and White[15] found the longest period of survival in this relatively asymptomatic group, 56 per cent of whom survived for at least ten years, and only 1 of whom developed congestive heart failure. When death eventually occurred in patients of this most favorable group, it was usually caused by another and fatal coronary occlusion or it came suddenly and unexpectedly.

Patients who are able to resume gainful employment after surviving the acute attack of myocardial infarction represent a larger percentage than the asymptomatic group because many who continue to suffer anginal pain or mild dyspnea are nevertheless able to work. According to Ball et al.,[7] 26 per cent of 253 patients who survived an acute myocardial infarction were able to return to their usual activity, and 21 per cent to resume lighter activity. More than two fifths of 500 patients who suffered a coronary occlusion and were studied by Master and associates[36] made a complete functional recovery, and 85 per cent of these resumed employment, 65 per cent full time and 20 per cent part time work. When activity was restricted, it was due to symptoms such as angina pectoris, dyspnea on effort or at rest, and weakness or easy fatigability. These symptoms individually or in combination are present in about two thirds of patients following acute myocardial infarction.[15]

Angina Pectoris

Occasionally, patients who have suffered from angina pectoris lose their pain after an attack of acute myocardial infarction, probably because the anoxic muscle responsible for the pain is no longer viable. Much more often attacks of angina pectoris on effort or at rest persist after cardiac infarction, and in about half of the cases in which angina pectoris is absent before the attack, it develops after recovery from the acute infarct. Palmer[10] observed angina pectoris in about 60 per cent of the patients who had recovered from an acute cardiac infarct, a higher incidence than before the attack. Furthermore, the attacks of angina pectoris usually occurred more often, and were more persistent and more readily induced by minor exertion or at rest than previously. Bland and White[15] found that one third of their patients who recovered from the acute attack were limited in their

activity by angina pectoris alone In this group only one third survived for ten years or longer as compared to 56 per cent in the recovered group without symptoms

Hypertension

The blood pressure remains at relatively normal levels in one third to one half of the cases in which hypertension existed before the attack [35] In the remainder the blood pressure gradually rises to a hypertensive level which is somewhat below that prior to the attack [101] According to Chambers [9] 58 per cent regain hypertension within two years Occasionally the blood pressure eventually exceeds that before the cardiac infarction In patients with normal blood pressure before cardiac infarction the blood pressure may gradually return to the previous level but often it is 10 to 20 mm lower and may even remain at hypotensive levels (below 100 mm)

Observations as to the influence of hypertension on the subsequent course of the disease including the development of heart failure and the duration of life are in disagreement but in my experience heart failure occurs more frequently and the outlook for life tends to be less favorable in those in whom hypertension recurs

Heart Failure

Dyspnea is a consistent complaint in more than half of the patients while objective evidences of heart failure usually of the left ventricle are observed in about one quarter of the patients Dyspnea restricted the activity of about one third of the patients followed by Bland and White[15] who had survived an *acute attack of coronary occlusion* This group pursued a much less favorable course than either those who were free from symptoms or even those who suffered from angina pectoris after their recovery from the acute attack None of them survived a ten year period and 75 per cent of the patients with dyspnea succumbed because of congestive heart failure It is interesting that symptoms or signs of left heart failure which appear in half to two thirds of the patients during the acute attack disappear in a majority of those who recover Occasionally dyspnea and angina pectoris are present in the same patient

Cardiac enlargement following recovery from myocardial infarction is observed in more than half the cases When it is of considerable degree it is associated with persistent and overt manifestations of congestive heart failure Consequently restriction of activity occurs much more regularly when cardiac enlargement follows myocardial infarction [m] Conversely a normal cardiac size following recovery from the acute attack usually promises a better clinical recovery and a favorable outlook for normal activity

Electrocardiographic Changes Following Recovery

The electrocardiogram returns to normal in about 15 per cent of cases usually within a year after the attack In the remainder Q waves inverted T waves or T waves of low voltage or slurred notched and prolonged QRS complexes persist without necessarily denoting an unfavorable prognosis In patients with a previous myocardial infarction a fresh infarction of the other wall may result in normalization of the electrocardiogram although usually evidence of one or both infarcts is apparent In a recent study of the electrocardiograms of 51 patients one year after an acute myocardial infarction Gittler et al found that return to a normal electrocardiogram occurred in only one case [60]

SUBSEQUENT ATTACKS OF CARDIAC INFARCTION

Regardless of the outcome after an acute cardiac infarction the further outlook for the patient is clouded by the danger of further episodes of coronary occlusion and cardiac infarction It should be emphasized that there is insufficient knowledge of the probability of subsequent attacks of myocardial infarction in any group to permit this knowledge to be used as a control basis to evaluate the influence of diet or any other therapeutic agent in preventing subsequent attacks Clinical studies suggest that such additional attacks recur in about 30 per cent of cases usually within two years after the first attack However pathologic studies attest to a much higher incidence of recurrent coronary occlusion These new episodes are often overlooked because the clinical features either are not as characteristic as those of the first attack or are overshadowed by symptoms and signs of congestive heart failure and because the electrocardiographic changes when superimposed on previous abnormalities are often not specific Each additional attack of cardiac infarction either increases the probability of a fatality or leaves the patient more subject to the development or intensification of congestive heart failure or disabling attacks of angina pectoris than after the first infarct

EFFECT OF PATIENT'S COOPERATION AND MORALE

In concluding this discussion of factors modifying the prognosis after cardiac infarction it is well to emphasize the importance of certain less easily measured influences These include the cooperation of the patient with his physician in making the necessary modifications in his diet in the use of tobacco, in his hours of sleep and rest and in the character and duration of his work or other activities without resentment or moroseness at his unfortunate fate The success with which these adjustments are accomplished is dependent in general on the patient's capacity for a healthy optimism and contented readjustment despite essential restriction and also in large measure on the wise and tactful management of an understanding reasonable and practical physician

TREATMENT OF ACUTE CARDIAC INFARCTION

The treatment of acute cardiac infarction is designed (1) to reduce the work of the heart until the infarcted area is healed (2) to alleviate pain or other discomfort, (3) to overcome shock and cardiac failure if present and (4) to cope with dangerous cardiac arrhythmias or any complications that may arise (For a detailed discussion of individual measures see below beginning p 562)

SYMPTOMATIC TREATMENT

Pain

As a rule *morphine or other opiates* (p 571) are administered to control severe *pain, restlessness and anxiety* at the onset of the attack but morphine is not essential if the pain is relatively mild and can be relieved by meperidine (Demerol) codeine or weaker analgesics If the pain has already subsided, none of these drugs need be used but mild sedatives may be advisable (p 579) If extremely severe pain is unrelieved by opiates, it may sometimes be controlled by oxygen therapy (p 570) and by the intravenous administration of aminophylline (p 285)

SHOCK

Prompt treatment is essential

General Measures

Certain general measures such as rest in bed and the alleviation of pain restlessness and anxiety by opiates are indirectly helpful But in the absence of pain and great restlessness opiates should be withheld, because they tend to depress pulmonary and tissue respiration, intensify the anoxia already present and interfere with diuresis The application of external heat to the extremities, other than by blankets adequate to preserve body warmth, is now considered of dubious value, if not detrimental, in the treatment of shock Furthermore external heat may intensify perspiration in patients who are already dehydrated from loss of fluids Oxygen is administered continuously by mask or in a tent Associated pulmonary edema or cardiac arrhythmias are treated by appropriate measures and anticoagulant therapy is instituted if there is no contraindication

Specific Measures

Ideally, specific agents employed for the treatment of shock should act directly on the heart to bolster the sharply reduced cardiac output which is responsible for the shock of myocardial infarction Usually they are intended to raise the mean aortic pressure and thereby secondarily benefit the heart by augmenting coronary perfusion pressure and coronary flow They are designed to enable the patient to survive a critical period until the heart recovers its ability to maintain the blood pressure without outside aid

Specific measures include (1) vasopressor drugs, (2) intravenous infusions of blood plasma or plasma expanders, (3) intra arterial transfusions

1 **Vasopressor Drugs** A number of vasopressor drugs which are sympathomimetic amines, closely allied in structure to epinephrine, ephedrine and paredrine, mark the first really encouraging advance in the treatment of shock in acute myocardial infarction [60 67 69 116] The preferred drugs are norepinephrine (Levophed noradrenaline), mephentermine (Wyamine) methoxamine (Vasoxyl) and phenylephrine (Neo-synephrine) Norepinephrine is most extensively used because it is the most powerful and because it can be most readily controlled and administered by intravenous drip transfusion for the prolonged periods of time that are frequently necessary *Aramine*[levo 1 (m hydroxyphenyl) 2 amino-1 propanol] a new long acting sympathomimetic amine which not only raises aortic pressure but also was shown to increase cardiac output and coronary flow by increasing cardiac contractility in dogs, also gives promise of therapeutic effectiveness [117]

The use of pressor drugs in shock is based on the belief that the sympathetic vasoconstriction of shock has not produced maximal increase in peripheral resistance and that these drugs can further magnify this resistance and raise the blood pressure. In this manner it is hoped that an adequate perfusion pressure is restored to vital organs such as the heart and brain and the diminished blood flow redistributed in favor of these organs. However, it is apparent that a rise in blood pressure despite an increase in peripheral resistance occurs only if there is an increased force of cardiac contraction in response to the increased work load. It is uncertain whether the increased peripheral resistance induced by vasopressor drugs is itself the adequate stimulus for augmented cardiac output or whether these drugs have a direct beneficial cardiac effect.

Recent studies actually indicate that norephinephrine and other pressor amines have such a direct action on the myocardium in shock. Sayen et al [118] noted that Levophed increased the oxygen tension of myocardium made ischemic by ligation of a coronary artery. Gazes and associates,[68] using strain gauge techniques in fully conscious trained dogs showed that l norepinephrine produced substantial increments in the cardiac contractile force, in addition to its recognized pressor effects. Sarnoff et al [117] observed that Aramine caused a sustained increase in myocardial contractility and increased cardiac output, ventricular work, aortic pressure and coronary flow, while left atrial pressure fell. These findings were interpreted to indicate that vasopressor drugs are effective in shock because of direct action in the heart as well as their pressor action.

l-Norepinephrine or l arterenol (Levophed) [66, 67, 24] Norepinephrine is two to three times as effective as epinephrine in augmenting coronary flow and possesses the advantages of not accelerating the heart rate or stimulating the nervous system or producing cardiac arrhythmias. In administering Levophed, care must be taken to avoid extravascular infiltration as it may result in severe necrosis and ulceration of the skin.

DOSAGE AND ADMINISTRATION Levophed is available in ampules containing 4 cc of a 0.2 per cent solution (or 8 mg) of Levophed bitartrate, equivalent to 4 mg of Levophed base. One ampule is dissolved in 1000 cc of 5 per cent glucose in distilled water (or physiologic saline if there is no objection to the sodium ion). The final dilution represents 8 micrograms of Levophed bitartrate or 4 micrograms of Levophed base per cubic centimeter of solution. This is administered intravenously by needle or polyethylene tubing through the necessary tubing with clamp, and a drip bulb to control the rate of flow. The latter is adjusted to maintain the blood pressure at about 100 mm Hg in most patients or 120 mm Hg in previously hypertensive patients. One may begin with a flow rate of 20 drops per minute but this may be hastened or retarded according to the blood pressure which is determined continuously or very frequently by a physician or nurse in constant attendance. If the rate of flow must be increased to more than 40 drops per minute, one or more additional ampules of Levophed are added to the solution or an additional flask with a higher concentration of Levophed is connected to the first flask by means of a Y tube.

As a rule one to four ampules of Levophed dissolved in the 1000 cc glucose solution running at the rate of 20 to 30 drops per minute (10 to 60 micrograms of Levophed bitartrate per minute) succeed in maintaining the blood pressure at the desired level, but occasionally much higher doses may be required for satisfactory response. Usually however if there is no satisfactory response to 60 micrograms of Levophed bitartrate per minute, higher concentrations will also prove ineffective but they should be given a trial if necessary. The rate of flow is also determined according to fluid requirements. If fluid restriction is necessary the concentration of Levophed can be increased and inflow regulated to provide no more than 500 to 1000 cc in 24 hours.

At first the concentration and rate of flow of the Levophed solution may require several changes, but usually the blood pressure can be stabilized at a desired level after a few hours without much modification of the solution or rate of flow thereafter. As the patient improves attempts are made to diminish the dosage of Levophed and finally to discontinue it. It may be necessary to maintain the Levophed for 12 to 36 hours commonly or occasionally for several days to a week.

RESULTS That Levophed is capable of raising and maintaining the blood pressure in cases of shock due to myocardial infarction is unquestionable Any doubt of this is dispelled by the numerous cases in which the blood pressure is so low that it cannot be measured in the brachial artery but is promptly elevated to 100 mm Hg or more by Levophed There after for a period of many hours or days the blood pressure repeatedly falls to zero each time an attempt is made to discontinue the drug, whereas there is a prompt restoration of adequate blood pressure when the drug is resumed Although a pressor effect following Levophed has been noted in 80 to 95 per cent of cases in most reports *persistent* relief of shock i e for twelve or more hours after the pressor drug is discontinued is attained less regularly, perhaps in 25 to 55 per cent of cases

The extent to which Levophed and similar pressor amines save lives is more difficult to evaluate [14] The rate of survival after nor epinephrine has varied according to different reports but in the larger series of cases the survival rate was 30 to 50 per cent The mor tality rate in cases of shock with acute myo cardial infarction is said to vary between 70 and 80 per cent Actually there is no satis factory control series which provides the desired information The criteria for shock are not well defined nor do all observers agree in the diagnosis in individual cases This is indicated by great differences in the reported incidence of shock in myocardial infarction In some series this incidence ranges between 45 and 55 per cent while in other series it ranges between 10 and 20 per cent of the cases of myocardial infarction These differences are clearly due to different criteria for shock since the average mortality is 80 per cent in the various series with low incidence of shock and only 35 per cent in those series with a higher incidence of shock It is apparent that the interpretation of the effectiveness of vaso-pressor drugs or other agents will depend on whether the control mortality rate from shock in myocardial infarction is taken to be 80 per cent or 35 per cent Fewer and more severe cases of shock will be included if one insists on systolic blood pressures of 80 mm Hg or less than if one accepts systolic blood pressures of 90 mm Hg or less as evidence of shock More cases and less severe ones will be included if pressures of 100 mm Hg are accepted as evi dence of shock in patients who were previously hypertensive Furthermore, hypotension, per se, is an inadequate criterion of shock unless there are also clinical manifestations due to inadequate blood flow and sympathetic stim ulation such as tachycardia cold moist skin, oliguria, and dulled sensorium In the ab sence of uniform criteria of shock in acute myocardial infarction or of controlled studies of mortality rate, the effectiveness of Lev ophed or other pressor amines in saving lives cannot be determined

Sampson and Zipser[118] reported that 20 (67 per cent) of 30 patients treated with norepinephrine survived the episode of shock and 16 (53 per cent) recovered clinically and were later discharged from the hospital The mortality rate was higher among patients who were in shock longer than three hours before therapy was instituted Griffith and as sociates[65] reported that shock was present in 161 (19 7 per cent) of 816 cases of acute myocardial infarction One hundred and twenty eight (80 per cent) of the patients with shock treated with various measures but not with pressor amines succumbed On the other hand, in a subsequent series of 134 cases of shock in myocardial infarction treated by pressor amines and other specific forms of shock therapy, the mortality rate was sub-stantially less viz 47 8 per cent More sig nificantly the mortality rate was only 13 per cent among 60 patients treated within three hours whereas the mortality rate was 76 per cent among 74 patients in whom specific therapy was instituted more than three hours after the onset of shock Of 30 cases treated with norepinephrine (Levophed) shock was controlled in 17 As in other forms of shock treatment of the shock of myocardial infarction is reported to be more effective the earlier the pressor drugs are administered On the other hand, in an undetermined number of cases, shock subsides spontaneously within one to three hours after onset or because of simple measures to relieve pain The ef fectiveness of early treatment may then ap pear to be influenced by the inclusion of cases in which shock would have subsided without the use of specific vasopressor drugs

Mephentermine (Wyamine) may be admin istered slowly by vein injecting 1 cc of Wyamine sulfate containing 15 mg of Wya

mine base as a priming dose [redacted] The drug is then given as a continuous intravenous infusion at the rate of 1 mg per minute and modified as desired Thirty to 75 mg of Wyamine base (2 to 5 cc) may be dissolved in 100 cc of 5 per cent glucose in water and administered by slow intravenous drip over a period of approximately an hour (15 to 20 drops per minute) The rate of flow and the concentration of the solution are regulated and modified according to the blood pressure which is checked continuously It is also possible to obtain and maintain a continuous pressor effect by the intramuscular injection of 15 to 30 mg at half hour intervals or longer I have used Wyamine chiefly to initiate treatment since it can be administered intramuscularly or intravenously without much dilution until Levophed dilution and set up can be arranged

Methoxamine (*Vasoxyl*)[88] This drug is administered intravenously in a dose of 5 mg or intramuscularly in a dose of 15 mg but the dose may be increased and repeated as necessary to attain and maintain the desired elevation of the blood pressure[38] It may be given as a continuous intravenous infusion containing 100 mg per liter at a rate determined by the blood pressure

Phenylephrine (*Neo-synephrine*)[1] is available in 1 per cent solution for parenteral use A dose of 5 to 15 mg (0 5 to 1 5 cc) may be given intramuscularly or 2 to 5 mg slowly intravenously as an initial dose followed by a continuous intravenous infusion at the rate of 2 5 mg of Neo-synephrine every 15 minutes

Isopropylepinephrine (*Isuprel*) is used only when shock is associated with complete heart block and Adams-Stokes syndrome It is given in a dose of 2 or 3 mg slowly intravenously and then [redacted] to 15 mg doses may be given sublingually at 10 to 30 minute intervals

Metaraminol (*Aramine*) has been administered by intravenous infusions of 50 to 200 mg per liter of 5 per cent glucose in water at the rate of 2 to 6 cc per minute [redacted] Following a single intravenous injection of 3 to 15 mg of Aramine a maximal pressor response is attained in five minutes and the rise in blood pressure persists for 25 minutes[128] Although Aramine is somewhat less potent than norepinephrine it possesses advantages of more prolonged action and greater ease of controlling its administration and dosage

Steroid Hormones Manchester[82] described 7 cases of acute myocardial infarction and severe shock unresponsive to vasopressor drugs Urine ketosteroid determinations and blood eosinophil counts indicated adrenal insufficiency which was attributed to the stress of myocardial infarction and prolonged shock Following the administration of hydrocortisone and desoxycorticosteroid together with adequate amounts of sodium and norepinephrine there was a dramatic vasomotor response and improvement

2 **Intravenous Infusions and Transfusions.** For a period of time infusions of plasma or small transfusions of 150 to 250 cc were advocated and used in the treatment of shock accompanying acute myocardial infarction[113, 41] Occasionally these appeared to be beneficial at least temporarily but it is doubtful that they had any significant influence on the outcome There is always a danger of inducing pulmonary edema although in most cases no such complication was reported If as is often the case pulmonary edema is already associated with the shock transfusions and infusions of plasma are contraindicated At the present time transfusions do not appear to be indicated because of the availability and superiority of the pressor drugs

3 **Intra arterial Transfusions**[1, 4, 13] These were designed to combat the cardiogenic shock of acute myocardial infarction by bringing blood directly where it is needed i e on the arterial side without overloading the weakened myocardium as intravenous transfusions are theoretically likely to do Actually if the circulation is maintained blood or other fluid introduced on the venous side reaches the arterial side and blood introduced intra arterially traverses the venous segment Recent controlled experiments in hemorrhagic shock have shown no statistical difference in the effectiveness of intravenous or intra arterial transfusions when the infusion rates were the same [redacted] [27, 68] However intra arterial transfusion of oxygenated blood appears of value in cases of shock with virtual cardiac stoppage in order to provide a priming elevation of arterial pressure and an adequate coronary perfusion pressure Thereafter pressor amines may be used to maintain the desired blood pressure A method of arterializing the blood and transfusing it intra arterially under pressure was described by Silber and associates[1, 4] Shock was controlled

in 3 of 9 cases of acute myocardial infarction, but only 2 survived. Two hundred and fifty cc of blood may be administered in 10 to 30 minutes at a progressively higher inflow pressure, up to 100 to 120 mm Hg. Arterial transfusions are rarely employed at present, because of the superiority of the pressor amines.

In summary, the intravenous administration of Levophed or other pressor amines represents the treatment of choice in shock accompanying acute myocardial infarction. These drugs are undoubtedly effective in restoring an adequate blood pressure in the large majority of cases. They probably also increase the chances of survival but there is less certainty regarding this point.

Shock and Pulmonary Edema

This combination occurs frequently and often poses a therapeutic problem. The shock may be treated as discussed with vasopressor agents but due regard must be paid to minimizing the quantity of intravenous fluids and using glucose instead of sodium chloride. In addition morphine, oxygen and intravenous aminophylline are administered as in the treatment of uncomplicated pulmonary edema. Digitalis may be injected intravenously (p. 262) if these measures are ineffective. Mercurial diuretics are given only after these emergency measures are completed. Phlebotomy is contraindicated in severe shock. Occasionally the control of shock by vasopressor agents with consequent improvement in cardiac function, abolishes pulmonary edema and the need for specific measures to counteract it.

ACUTE LEFT VENTRICULAR FAILURE

In the presence of acute left ventricular failure characterized by pulmonary edema, immediate and sometimes drastic therapeutic measures must be instituted (p. 292). Morphine or other opiates should be administered subcutaneously as indicated in order to control intense dyspnea as well as anxiety or pain. If morphine is ineffective the *slow intravenous injection of 0.5 gm. of aminophylline* in 20 cc. solution may control pulmonary edema.

While the question of using *digitalis or strophanthin* in acute left ventricular failure due to cardiac infarction is moot (see below, p. 579), dramatic relief of acute pulmonary edema sometimes follows the intravenous injection of 0.25 mg. (1/240 grain) of ouabain (p. 258), repeated if necessary in one-half hour to one hour, in patients who have not received digitalis in the previous two weeks. Under less urgent circumstances, 4 cc. of Cedilanid may be administered intravenously.

Oxygen should be administered in high concentration (80 per cent or more), or preferably under positive pressure[8] but only if there is no shock. Usually this measure is effective in controlling the anoxemia and cyanosis associated with severe pulmonary edema.

Rotating tourniquets on the four extremities should be used, as in other cases of pulmonary edema (p. 292).

In extreme cases of pulmonary edema with increased systemic venous pressure, the removal of 350 to 500 cc. of blood may be lifesaving when all other measures have failed but this should not be performed if there is severe anemia.

INDIVIDUAL THERAPEUTIC MEASURES AND DRUGS

Bed Rest

It was formerly thought that patients suffering from an acute myocardial infarction should be put to bed for an average period of four to six weeks. Rest is a traditional principle of treatment of a diseased organ, and as applied to the heart is intended to diminish its work. This recommended rest period is based on relatively limited pathologic studies which indicate that six weeks are required for the infarct to be converted into a firm scar[80] and experimental studies showing that two or three weeks are necessary for the development of a collateral circulation to supplement the interrupted blood supply.[■ 11] It seems unreasonable, however, that the same fixed period of bed rest should be prescribed for all patients with acute myocardial infarction whether they are critically ill or asymptomatic after a brief episode of pain, whether there be relatively high and prolonged fever or slight fever for only a few days, and whether or not they suffer from shock, pulmonary edema, congestive heart failure or serious complications.

Most of the fatalities and complications from acute myocardial infarction occur during the first week, a more moderate number in the second week and relatively few in the third week. For this reason, it is my policy to recommend a minimum of two to three weeks of rest in bed. But, as discussed below, this

does not mean complete immobility or even complete restriction to bed for every minute of that period. For an additional period of three to four weeks (making an average total of six weeks) the patient is confined to bed part or most of the time. But within the confines of his bedroom or his hospital room he is permitted moderate liberties which do not involve more than the simplest exertions and do not result in mental or emotional strain.

This average period of six weeks is designed to permit recovery from the acute attack and permit healing of the infarct. It does not include a further period of weeks or months of convalescence to permit the gradual resumption of a permanent routine. Furthermore, this average period does not allow for the occurrence of complications, the development of chronic left- or right-sided heart failure, frequent attacks of angina pectoris, or extreme weakness, which may extensively prolong the period of rest in bed or of greatly limited activity.

The rigid severity with which bed rest was enforced has led to considerable public expression with regard to the dangers of the exaggerated application of this therapeutic measure. It has long seemed quite reasonable to assume that "complete rest" is desirable for the acutely infarcted heart muscle until healing ensues. Physical exertions have been feared because of the risk of rupture of the softened myocardium. Myocardial infarcts produced experimentally in dogs were found to heal with a small strong scar when the dogs were rested for six days after infarction, whereas aneurysmal bulging and a thin scar resulted if the dogs were exercised in the first three days after infarction.[2,3] On the other hand, it may be questioned whether most patients would be harmed by such simple activities as feeding themselves or using a commode instead of a bedpan, or even going to a nearby bathroom once daily for a bowel movement. Moreover, the advantages of bed rest must be weighed in individual cases against the deterioration of morale, the frequency of constipation and abdominal distention, the circulatory strain often involved in the use of the bedpan, the occurrence of disabling muscular and ligamentous strains, especially of the back or the shoulders, the development of bedsores, the risk of decalcification of the bones, especially in the elderly, and the occurrence of urinary disability if not retention in patients with moderate prostatic hypertrophy.

If patients with orthopnea, cardiac asthma, or pulmonary edema are forbidden to sit in a chair or upright in bed, disability is increased. The disadvantages of recumbency to such patients have been mentioned (p. 194). The dangers of hypostatic congestion and bronchopneumonia increase with the degree of immobility of the patient. But most important of all, pulmonary embolism, one of the very common causes of death from myocardial infarction, may be attributed primarily to venous stasis and thrombosis of the leg veins caused by strict and prolonged bed rest. Pulmonary embolism is sometimes precipitated by extreme straining at stool, and this danger is enhanced in many patients who are forced to use the bedpan even when this necessitates excessive straining.

These considerations should lead to careful reflection before ordering complete bed rest for a fixed period of time as soon as the diagnosis of acute myocardial infarction has been made. It has long been my custom to permit patients to feed themselves, to move freely in bed, and to perform leg exercises (especially dorsiflexion of the feet with contraction of the calf muscles) at regular frequent intervals as soon as possible after the onset of the attack. If the patient is capable of using the commode and has found real difficulty in using a bedpan, I have permitted the former. Most patients are permitted to use the lavatory once daily at a regular time for a bowel movement. Above all, management should be sufficiently elastic to permit desirable modification in individual cases. The recent tendency to liberalize the meaning of bed rest in cases of myocardial infarction will prove to be beneficial only if it does not lead to the opposite extreme of utterly neglecting this fundamental therapeutic measure.

Rest in bed for the patient recovering from acute myocardial infarction means not only avoidance of physical exercise but complete mental repose and protection from emotional strain. These aims cannot always be fully realized, but as far as possible they should be attained by isolation of the patient from outside communications and contacts which produce mental strain or upset him emotionally, by confident reassurance that he will get well

by efficient examination and care of the patient on the part of the doctor and nurse with as infrequent disturbance as possible and by sufficient medication to keep him free from pain or other discomfort and to provide adequate sleep

Armchair Treatment[70, 143, 85, 11]

If complete bed rest is associated with disadvantages and even with danger, it does not follow that no bed rest at all is preferable Nevertheless it has been recommended that patients with acute myocardial infarction be treated continuously in a chair during waking hours, except in the presence of shock or extreme debility Improvement of morale relief of orthopnea and avoidance of pulmonary embolism are some of the claimed advantages A diminution in cardiac output and in the work of the heart in the sitting position is another listed benefit of chair treatment

Many patients do prefer sitting in a chair to lying in bed after the first few days but few of them prefer sitting in a chair all day long if they are not allowed to get up and walk about Patients with orthopnea are more comfortable sitting in a chair than lying *flat* in bed, but not necessarily more comfortable than when they sit up in bed But this claimed advantage of chair treatment indicates a confusion between *recumbency* and *rest* The problem of recumbency or upright position is not really directly related to the treatment of acute myocardial infarction It is a problem in the management of left-sided heart failure with orthopnea or cardiac asthma There has not been and there *is no question about* permitting the patient who is orthopneic to maintain an upright position in bed, at the side of the bed, or in a chair until such time as the heart failure is controlled This has nothing to do with the problem of bed rest versus chair rest in acute myocardial infarction per se

The claim that chair rest may prevent pulmonary embolism is also based on a confusion—between *chair treatment* and *early ambulation* Although early ambulation in acute myocardial infarction, as in postoperative management may reduce the incidence of thromboembolic complications there should be no pretense that chair treatment means early ambulation Rather, at least on theoretical grounds, one would anticipate that chair treatment would predispose to stasis and phlebothrombosis in the lower extremities and to consequent pulmonary embolism

Assumption of the upright position reduces the venous flow and the cardiac output and hence the work of the heart Little is known about the effect on the cardiac output of a prolonged stay in the sitting position We know of course the advantage of diminishing the venous return in patients with pulmonary congestion in left sided heart failure, but this is not the particular problem in most patients with acute myocardial infarction Much of the difficulty in the latter is due to an inadequate cardiac output, one may therefore question the advantage of further reduction in the cardiac output The problem of reducing cardiac work in treating coronary thrombosis may be less important than the problem of cardiac work in relation to coronary blood supply The sitting position would not be advantageous if the coronary flow were diminished more than the cardiac work There is evidence that blood flow to the brain and kidneys is diminished in the upright position Perhaps there is a similar effect upon the coronary circulation It is apparent that there is much to be learned or proved before we invoke physiologic arguments to support our prejudices for either bed rest or chair treatment

It is apparent that the outcome in the vast majority of cases of acute myocardial infarction will not be determined primarily by the use of bed rest or chair treatment Recovery or a fatal outcome probably depends chiefly on the nature and severity of the myocardial injury and the response of the heart and other organs to that injury Repeated references to the 'dangers' 'abuse' and "myth' of bed rest have served to call attention to the need for reexamination of the basis for a long standing axiom But it would be unfortunate if these discussions distracted us from grappling with the more important factors in mortality from acute myocardial infarction Bed rest, especially when intelligently carried out modified and individualized, is not a significant factor in this mortality, neither is chair treatment the cure Sitting in a chair for limited periods for patients who can profit from such change in position, as part of an elastic individualized program of bed rest, is certainly permissible or desirable, sitting in a chair throughout the day, as a rigid prescribed form of therapy, is not recommended

Hospital versus Home Care

Most patients with acute myocardial infarction can be treated satisfactorily at home. Hospitalization may be preferable when certain measures such as oxygen therapy and anticoagulant therapy are essential and cannot be properly carried out at home, when the patient's home is at a considerable distance from his physician and the severity of the attack and its complications warrant frequent and prompt medical attention, when satisfactory dietary or nursing care cannot be obtained at home, when the patient's activities or intrusions by relatives, friends or business associates can only be controlled in the hospital, or when other environmental conditions at home are undesirable. The patient's progress as determined by frequent observation and by electrocardiographic or other laboratory tests can usually be followed more easily and complications treated more promptly at a hospital. If for any of these reasons hospitalization appears preferable, the physician should not be deterred by the exaggerated fear of moving the patient, provided this can be done by ambulance with the aid of trained attendants. An opiate should be administered before transporting him, and other available emergency measures instituted if necessary.

Sometimes hospitalization appears preferable to home treatment for the first two or three weeks, after which treatment may be continued at home. Under these circumstances also there is no objection to moving the patient if he is recovering satisfactorily and if no excessive exertion on his part is required in the transfer, which should be by ambulance.

Nursing Care

Good nursing care can be a valuable adjunct to treatment. Its purpose should be to help the patient avoid undesirable exertions, to protect him from the telephone and from visits by his business associates, friends and relatives, and to provide a cheerful atmosphere, as well as to administer medications and other therapeutic measures. As indicated above, "too good" nursing may be fraught with danger if it involves complete restriction of the patient to the point where he lies in bed like an inanimate log.

Diet

In the first week the diet must be varied according to the patient's condition. When severely ill he may take only small amounts of fluid at a time, such as fruit juices, milk, broth, tea, ginger ale or water. Care should be taken to avoid distressing abdominal distention in persons intolerant to milk or excessive amounts of fruit juice. Some patients who tolerate milk may be given the Karell diet (200 cc. of milk every four hours) for 24 hours or longer. Sodium intake should be restricted if there is evidence of congestive heart failure.

If there is persistent vomiting during the first day or two, 50 cc. of 50 per cent glucose can be given intravenously at regular intervals to provide fluids and carbohydrate, or a continuous infusion of 5 per cent glucose in distilled water may be given. These are discontinued as soon as fluids can be taken orally.

As soon as they are tolerated, soft foods are given in addition to fluids. Cooked cereal, soft boiled egg, milk toast, stewed fruit, junket, mashed or baked potato and simple puddings may be given at brief intervals if necessary, but only in small amounts at any one time.

When the very acute symptoms have subsided (or in mild cases from the very onset) I allow between 1000 and 1200 calories daily and increase this gradually as the patient is permitted to get out of bed and resume moderate activity.

The diet should eliminate foods which are usually difficult to digest, which are likely to cause distention or to which the patient has a sensitivity or special aversion. Raw fruits, fruit juices in excess, fried foods and gravies, spices and condiments, onions, corn, members of the cabbage family, pastries, chocolates, corned or smoked meats and fish, fatty meats and fish, cheeses, nuts, dates, figs and raisins should be avoided. The intake of salt should be minimized in the presence of congestive heart failure.

When the patient resumes moderate activity, his caloric intake should be such as to maintain his weight if it is normal, or to reduce it if he is overweight. Whenever feasible the daily caloric allowance should be divided into five meals to avoid an excessive quantity at any one time.

In the presence of diabetes mellitus, the caloric allowance should be apportioned properly among carbohydrates, proteins and fats. Insulin is discussed below.

For a discussion of diet in relation to the underlying *atherosclerosis*, see page 436.

Tobacco Alcohol, Coffee

Coffee in moderation is allowed if it does not increase restlessness or cause sleeplessness *Alcohol* is usually permissible if the patient desires it or is accustomed to it It has long had the reputation of clinical benefit in angina pectoris and often appears to benefit the patient during convalescence from an acute myocardial infarction However I do not prescribe it for patients who do not take alcoholic drinks ordinarily or who dislike it To patients who complain of weakness or depression and especially to elderly patients I often suggest a trial of alcohol in doses of 15 to 30 cc (½ to 1 oz) repeated twice daily, its continuation is dependent on the patient's subjective reaction The alcohol is given in the form of whiskey, brandy sherry or other wine Wine sherry and beer often act as satisfactory soporifics Alcoholic beverages should not usually be prescribed if there is prostatism, and they often are detrimental to other possible associated conditions such as definite sinusitis, peptic ulcer gout, and irritable colon

Despite uncertainty as to the effect of tobacco in cases of myocardial infarction, I usually prohibit its use (p 416)

Care of Bowels

After a severe attack it is undesirable that the patient be disturbed or urged to move his bowels for the first three days as straining at stool may be a dangerous exertion Usually the patient is constipated during this period because of the low intake of food and especially because of the administration of opiates Soft easy bowel movements may be effected thereafter with the aid of mineral oil (*½ to 1 oz on retiring) and if necessary* small doses of milk of magnesia (½ to 1½ oz) each night If there is distention a small saline enema may be given preferably after mineral oil with or without a small dose of milk of magnesia has been administered on the previous night A rectal tube may also be used to help control distention

Whenever obstipation abdominal distress and distention are associated the possibility of a fecal impaction induced by opiates should be considered and a rectal examination made If present the impaction should be relieved manually

Oxygen Therapy (see also p 288)

The administration of oxygen has become an important therapeutic measure in the management of acute cardiac infarction However its usefulness is probably limited to relatively severe cases Levy and Barach[75] have reported striking relief of pain and restlessness slower and less labored respiration, diminution or abolition of cyanosis disappearance of Cheyne-Stokes respiration and other objective signs of improvement within one to three hours after beginning the administration of oxygen Unfortunately for its evaluation all of the dramatically favorable results observed in individual cases following oxygen therapy can be matched by a similar sequence of events in other cases without the aid of oxygen

Cyanosis is the clearest clinical indication for oxygen therapy, but mild degrees of cyanosis are easily overlooked clinically, and in the presence of shock cyanosis may be manifested as a grayish or ashen hue Borden et al[17] found the mean arterial oxygen saturation to be 94 1 per cent in a group of patients with myocardial infarction without pulmonary edema or shock, and 80 8 per cent in those with pulmonary edema or shock Oxygen therapy is often useful for acute pulmonary edema, especially when supplied by the positive pressure technique[8] Oxygen, without positive pressure is administered during shock Persistent dyspnea is a more definite indication for oxygen therapy but has not always been effectively controlled by it Dramatic relief from intractable pain has been reported by some observers I have yet to note such an impressive and fortunate occurrence although I have occasionally witnessed the partial amelioration of severe pain and the relief of mild pain by oxygen therapy *It should be emphasized that coronary occlusion results primarily in anoxia confined to* the affected myocardial tissue which cannot usually be significantly altered by the administration of oxygen

In practice it has been my custom to give oxygen therapy a trial in all cases in which there is severe or persistent pain, dyspnea cardiac asthma, pulmonary edema, shock, Cheyne-Stokes respiration and of course cyanosis This therapy is continued if there is any evidence of objective or subjective improvement of the symptom for which it was administered As the patient improves and the oxygen is discontinued it is promptly resumed if there is evidence that the patient was more comfortable during its administra

tion or if objective signs reappear which had been abolished by the oxygen

When the indication for oxygen therapy is clear cut I prefer to use an oxygen tent supplying a concentration of 50 to 60 per cent of oxygen when the latter runs in at the rate of 9 to 10 liters per minute The temperature in the tent which together with the humidity should be carefully regulated to the patient's comfort is usually maintained between 60 and 68 F If a tent is not available or if the patient is not easily managed in the tent oxygen can usually be administered satisfactorily by means of (1) a BLB mask (provided for oronasal or nasal breathing with a regulator which can deliver up to 100 per cent oxygen) (2) small transparent plasticele face tents which with a flow of 8 liters per minute can deliver a concentration of 40 to 60 per cent or (3) a bilateral nasal or a unilateral oronasal catheter The latter will provide about 35 per cent oxygen if the flow from the tank is 5 liters per minute but it is not usually tolerated by the patient

Drug Therapy

Morphine Morphine or one of its substitutes is the drug of choice in cases dominated by pain and restlessness paroxysmal or constant dyspnea or pulmonary edema The usual dose is 15 mg (¼ grain) hypodermically but it may be given intramuscularly when more rapid action is desired Often this dose must be repeated in one-half to one hour if the symptoms are not alleviated as much as 60 mg (1 grain) over a period of four hours may be required in extreme cases But not more than this total should be given within 12 hours In extreme cases a prompt effect may be obtained by giving 15 mg of morphine diluted in 5 to 10 cc of sterile water into a vein but respirations should be observed carefully and the injection stopped if the desired result is obtained before the full dose has been administered

Nalorphine (*Nalline*) *hydrochloride* should be available for treatment of excessive narcosis or respiratory depression Five to 10 mg of Nalline is given intravenously if the respiratory rate falls below 12 per minute and the dose may be repeated in 15 minutes if necessary Coramine (1 to 3 cc of a 25 per cent solution intravenously) or Metrazol (100 to 300 mg in ampules of 1 or 3 cc of a 10 per cent solution) may be used for the same purpose but are less effective *Aminophylline* is the drug of choice for Cheyne-Stokes respiration due to respiratory depression (p 285)

Because of the respiratory depression which morphine causes large doses must be given with caution and the patient observed carefully Standing orders for morphine with the decision as to its further use left to a nurse should not be countenanced It should also be emphasized that morphine should not be given routinely as soon as the diagnosis of myocardial infarction has been made Mild pain can often be controlled by Demerol or codeine and in some cases even these analgesics are unnecessary Even if morphine appears desirable 10 mg doses (⅙ grain) often suffice after the initial larger dose Aside from its tendency to depress or paralyze the respiratory center morphine has other disadvantages due to its constriction of smooth muscle and vagal stimulation The former results in pronounced constipation which may be extremely distressing and in predisposed persons in urinary retention due to spasm of the sphincter of the bladder The vagal stimulation poses at least the theoretical danger of causing coronary vasoconstriction and of rendering the heart muscle susceptible to ectopic ventricular rhythms

Other Opiates and Analgesics In my experience most patients vomit after receiving morphine and I have usually substituted *Dilaudid* which causes vomiting much less frequently Dilaudid is a synthetic drug related to morphine with proportionally more analgesic and less soporific and respiratory depressant effect Its therapeutic dose is about ⅕ that of morphine Usually 3 mg (1/20 grain) is approximately equivalent to 15 mg (¼ grain) of morphine

Pantopon which is a mixture of opium alkaloids containing chiefly morphine is said to cause vomiting infrequently but in my experience it induces vomiting as often as does morphine The dose of 20 mg (⅓ grain) of Pantopon is about equal to 15 mg (¼ grain) of morphine It is probable that its effectiveness is due entirely or almost entirely to the morphine it contains and for this reason it is associated with the same disadvantages and toxicity Methadone (Dolophine) 5 to 10 mg hypodermically is equivalent to morphine in its analgesic effect but is less sedative less narcotic and less likely to cause mental confusion

Demerol (meperidine) is a synthetic analgesic, chemically related to morphine and atropine It may be substituted for morphine after the early severe pain subsides and more moderate pain persists or recurs frequently after the first day But in many cases Demerol alone suffices to control the pain from the very outset Unlike the above opiates it does not result in respiratory or profound cerebral depression It is administered orally, hypodermically or intramuscularly in doses of 75 to 100 mg and may be repeated if necessary at four to six hour intervals Its effect is usually observed within 20 minutes after intramuscular injection and 30 minutes after oral administration In the above dosage it is more effective than 1 grain of codeine and does not have the constipating effect of codeine or morphine

Codeine in doses of 0 03 to 0 06 gm (½ to 1 grain) hypodermically or orally may also be substituted for morphine when the severe pain lessens or if the pain is moderate from the beginning

Anticoagulants *Evaluation and Indications*[109, 110, 111] Although it is now ten years since anticoagulants have been recommended and extensively used in the treatment of acute myocardial infarction, there is a persistent disagreement as to their effectiveness, their indication and as to the choice of patients to whom they should be administered[122] This dispute is the more remarkable since objective statistical studies show an unusually consistent advantage in favor of those patients who receive anticoagulants, with respect to both mortality and the occurrence of thromboembolic complications Why then the conflict? The answer must be discussed with respect to two distinct issues (1) Do the anticoagulants benefit the clinical course and outcome in acute myocardial infarction sufficiently to justify their use despite the risks involved? (2) Assuming the effectiveness of anticoagulants, should they be used in all cases of acute myocardial infarction or may they be omitted in a large group of so-called mild cases in which the mortality rate is relatively low?

1 *Do anticoagulants benefit the clinical course and outcome?* The rationale for the administration of anticoagulants is based on (a) the probability that thrombosis is less likely to occur if clotting of the blood is impaired, (b) experimental evidence that mural thrombi formation and extension of coronary thrombosis in dogs could be prevented by anticoagulants,[126] (c) evidence that a substantial portion of the mortality from acute myocardial infarction is due to extension of a coronary thrombosis, cardiac mural or peripheral venous thrombosis and embolism, and the thought that these thromboembolic phenomena might be minimized by anticoagulants, (d) statistical evidence in controlled series of clinical cases of acute myocardial infarction showing a highly significant reduction in the incidence of thromboembolic complications and in mortality rate when anticoagulants were administered[129] None of these is conclusive The process of intravascular thrombosis is complex and its mechanism still uncertain, anticoagulants whose action is measured by "prothrombin time" in vitro have not been shown definitely to control intravascular thrombosis Likewise the experimental evidence is not regarded as transferable to the human disease Therefore the case for anticoagulants rests essentially on clinical tests comparing the mortality rate and the incidence of thromboembolic complications in comparable series of patients with acute myocardial infarction who do and do not receive anticoagulants

Such studies have almost universally presented data attesting to a notable reduction in thromboembolic complications and in mortality associated with the administration of anticoagulants Following early favorable reports, the possible value of anticoagulants in acute myocardial infarction was investigated by a committee of the American Heart Association on anticoagulants, which reported on a cooperative study of 1031 cases in 16 hospitals[130] There was a mortality of 16 per cent in the patients treated with anticoagulants in contrast with a mortality of 23 4 per cent in the control group during the period of observation When the death rates were considered for the period of effective anticoagulant therapy, namely from the fourth day of anticoagulants through four days after the last dose the contrast was even more striking the mortality rate was 9 5 per cent for the treated and 17 4 per cent for the control group Evidence that the reduction in deaths was due primarily to anticoagulant therapy and not to any difference between the two groups is provided by the observation that the contrast in death rates occurred dur

ing the weeks when coverage with anti coagulants was most complete whereas during the remainder of the six week period of observation deaths in the control and treated groups differed insignificantly This interpretation is also supported by the observation that 42 per cent of the deaths in the control group and only 23 per cent of the deaths in the treated group were preceded by clinically diagnosed thromboembolic complications In terms of the total number of cases this contrast is even more striking for death preceded by a thromboembolic complication occurred in only 2 2 per cent of the treated as compared with 7 per cent of the control cases during the period of presumed effective anticoagulant therapy

Finally a review of 21 other controlled studies[180] of the use of anticoagulants in myocardial infarction involving 2812 cases revealed a similar favorable effect since the mortality rate was 14 8 per cent in the treated cases and 29 5 per cent in the controls These findings were consistent in that the results favored the use of anticoagulants in 19 of the 21 studies showed no advantage in one study and a disadvantage in only one In the one series in which the mortality rate was said to be unaffected by anticoagulants[181] there was no actual control series in the one series with a higher death rate in the treated cases there was a bias in the selection of cases since the anticoagulant was administered out of turn to some of the more severely ill patients[22] Even more impressive than the consistently favorable results in cases treated with anticoagulants is the consistency in the quantitative results in the various series a large majority (16 of the 21 series) showing a higher mortality rate of 50 to 200 per cent in the control over the treated cases

A recent analysis of anticoagulant-treated and untreated fatal cases of acute myocardial infarction examined at autopsy confirms the clinical observations on the advantages of anticoagulants[30b] The incidence of embolic complications in these fatal cases treated with anticoagulants was only 9 per cent in contrast with an incidence of 41 per cent among the untreated cases Similarly there was a marked reduction of thrombophlebitis and fewer mural thrombi in patients receiving anticoagulants These observations are especially important because embolic phenomena are often overlooked clinically hence clinical studies are less likely to reveal the benefits of anticoagulants in the prevention of embolic complications

In the light of these findings the indication for and effectiveness of anticoagulants in the treatment of acute myocardial infarction appear unassailable Whatever rationalizations may be offered to justify their omission the most potent objection is the trouble and expense involved in obtaining prompt accurate determinations of prothrombin time In addition there is often anxiety as to the risk of bleeding due to inaccurate prothrombin determination improper dosage of anticoagulant or unusual sensitivity of the patient Much of the opposition to anticoagulants would disappear if a simple accurate bedside method for determination of the prothrombin time became available The capillary blood prothrombin test proposed by Manchester[92] is a step in this direction but is still too difficult to perform accurately without great skill and experience

Another objection raised to the reported studies indicating effectiveness of anticoagulants is the serious difficulty of matching control and treated cases There is a great variability in the severity of cases of acute myocardial infarction and the results will depend in great measure on severity regardless of the treatment employed It is also difficult to assess the influence of anticoagulants on thromboembolic complications because of the imperfect criteria for their clinical diagnosis

2 *Should anticoagulants be administered in 'mild' as well as severe cases of acute myocardial infarction even assuming that they are of important benefit in the latter group?*

'Mild' or good risk cases selected from hospital records were found to have a death rate without anticoagulants of 3 1 per cent and an incidence of thromboembolism of 0 8 per cent[132] Cases of acute myocardial infarction were classified in the good risk category *if there were none of the following* (1) previous myocardial infarction (2) intractable pain (3) extreme or persistent shock (4) significant enlargement of the heart (5) gallop rhythm (6) congestive heart failure (7) arrhythmias such as atrial fibrillation or flutter ventricular tachycardia or intraventricular block (8) diabetic acidosis or other states predisposing to thrombosis Other studies have indicated that the mor

tality rate in first attacks of acute myocardial infarction in patients treated at home (presumably because they are mild cases) is only 3 to 8 per cent[6] [illegible] [11] Based on these varied observations it has been concluded that the mortality rate and incidence of thromboembolism in so called "mild" or "good risk" cases are so low that anticoagulants cannot be expected to improve the outlook significantly and any slight benefit is neutralized or outweighed by the complications of anticoagulant therapy[111]

Both the evidence and logic leading to this conclusion are subject to criticism The validity of the data drawn retrospectively from hospital charts has been challenged There is uncertainty as to the reliability of any criteria for determining prognosis *in the individual patient* on the first day of his acute attack This is when anticoagulant therapy should be begun if it is to be given I have frequently observed patients from whom anticoagulants have been withheld because they were labeled "mild" on the first day but who later fell into the poor risk category because of serious complications In a study of 107 patients with acute myocardial infarction,[57] the prognosis was ventured after 24 hours and again after 48 hours The initial decision as to "mild" or "severe risk" was reversed in 31 cases (30%), emphasizing the difficulty of evaluation when the patient is first observed in the early stage of the disease Francisco and Wright[45a] reported a high incidence of serious thromboembolic complications among so-called "good risk" cases of acute myocardial infarction There is need for further study of one's accuracy in distinguishing so-called "good risk" cases at the very onset of the illness

Perhaps it is the use of the term "mild" or "good risk" that [illegible] most misleading No disease that is associated with 5 per cent mortality can be called mild If anticoagulants are beneficial in very seriously ill patients with myocardial infarction, what evidence [illegible] there that they may not be significantly beneficial also in somewhat less seriously ill patients?—for a patient with [illegible] 5 per cent possibility of dying [illegible] seriously ill If anticoagulants can reduce the mortality in these cases by one third to two thirds, the saving cannot be disregarded if one is concerned with the individual patient Neither [illegible] there adequate evidence to indicate that the hemorrhagic complications of anticoagulant therapy result in fatalities sufficient to neutralize or outweigh their possible benefits There is obviously need for controlled studies to determine the comparative mortality rate with and without anticoagulants in the so-called "good risk" category of patients Thus in a study reported by Burton,[25b] there was a mortality of 2 per cent and thromboembolic complications occurred in [illegible] per cent of 156 "good risk" cases treated with anticoagulants whereas the mortality rate was 5 per cent and the incidence of thromboembolic complication was 11 [illegible] per cent among 58 "good risk" cases not treated with anticoagulants

CONCLUSION The over all mortality rates in controlled studies of anticoagulant therapy in acute myocardial infarction strongly suggest that anticoagulants should be employed routinely in this disease The difficulties imposed by great variability in the severity and clinical course of cases of myocardial infarction and the problem or impossibility of exactly matching control and treated cases necessitate some reservation as to the significance of the statistical evidence However, for the present, the weight of statistical *evidence* if not opinion is so uniformly favorable to anticoagulant treatment that good medical practice requires every physician to employ it Omission of anticoagulants is justified only by lack of laboratory facilities to perform accurate prothrombin determinations or by the presence of firm contraindications (infra) The difficulty and expense of "prothrombin" determination point to a need for correction of these defects, not for rejection of anticoagulant therapy

It has been proposed that in certain cases not associated with the most unfavorable features and euphemistically termed "mild," the possible advantages of anticoagulant therapy are relatively small and do not justify its risk, its trouble and its costliness Until it can be demonstrated that "good risk" cases can be accurately and consistently distinguished at the very onset of the illness, and until controlled studies of such "good risk" cases with and without anticoagulant therapy disclose no advantage of anticoagulants in these cases I prefer to assume that if anticoagulant therapy is beneficial in the treatment of seriously ill patients this benefit

should also be afforded to those who appear less seriously ill

Toxicity of Anticoagulants HEMORRHAGIC PHENOMENA AND TREATMENT The only important risk of anticoagulant therapy is that of hemorrhagic manifestations As a rule hemorrhagic complications can be avoided by careful control of the dose of anticoagulants according to a reliably determined prothrombin time Furthermore attentive clinical supervision should limit hemorrhagic manifestations to minor ones which are discovered early and promptly controlled by reduction or omission of anticoagulant or by the administration of vitamin K_1 Careful questioning and clinical and laboratory evidence of bleeding are important because occasionally bleeding occurs when the prothrombin time is reported in the therapeutic range Conversely there may be no evidence of bleeding in some cases despite prolongation of the prothrombin time well beyond the usual therapeutic range

Early evidence of bleeding tendency may be disclosed by black and blue marks with minimal trauma or unusual bleeding from minor cuts during shaving or from the gums after brushing the teeth Hematuria is one of the commonest manifestations of anticoagulant overdosage Before hematuria is discovered renal bleeding usually produces abdominal pain or classic ureteral colic The pink color of the urine produced by phenindione (Hedulin or Danilone) should not be confused with hematuria Gastrointestinal bleeding (often producing tarry stools) epistaxis and hemoptysis are overt signs of excessive anticoagulant dosage The occurrence and localization of bleeding in anticoagulant therapy is often determined by preexistent organ disease Thus gastrointestinal bleeding is apt to occur in an individual with peptic ulcer bleeding may be started from an ulcer which has been asymptomatic for years Hemoptysis appears to occur more readily when myocardial infarction is complicated by marked pulmonary congestion or recent pulmonary edema Hemorrhagic pleural effusion occurs not infrequently I have seen a hemopericardium in at least five cases in which I have performed a pericardial tap and suspected it in others In all of these there was evidence of excessive anticoagulant therapy and also evidence of pericarditis at the onset of the myocardial infarction Myocardial rupture and hemopericardium appear to be occurring more frequently since the use of anticoagulants[137] (p 543)

When there is only minimal tendency to bleeding anticoagulant effect may be maintained at more moderate therapeutic levels by omitting the dose for a day or two But if bleeding is more serious or if there is no wish to continue anticoagulation the prothrombin time may be restored to therapeutic levels in 4 hours and to normal within 24 hours by the administration of vitamin K_1 Transfusions of blood are given only for excessive blood loss

PHYTONADIONE (MEPHYTON K_1)[1 8 11] This is a commercial synthetic preparation of vitamin K_1 a 2 methyl 3-phytyl 1-4 naphthaquinone available as a 5 per cent aqueous emulsion in 1 per cent lecithin for intravenous use It must be kept cool and protected from the light It is far superior to the water soluble vitamin K_1 preparations as treatment for excessive hypoprothrombinemia Its method of action is unknown but after its administration bleeding due to hypoprothrombinemia ceases in 2 to 4 hours and may be partially controlled in 15 to 30 minutes A safe prothrombin time is attained in 3 to 6 hours and the prothrombin time is restored to normal in 8 to 14 hours For actual bleeding Mephyton is administered slowly intravenously in a dose of 50 mg (1 cc) in a period of 1 to 2 minutes Blood may be drawn up into the syringe mixed with the emulsion and the injection is made If there is significant blood loss the blood may have to be replaced by transfusion For minor hemorrhage only 10 mg of Mephyton need be given orally if anticoagulant treatment is to be continued Only 0 5 to 2 5 mg orally may suffice to reduce a prolonged prothrombin time (without bleeding) to therapeutic levels Restoration of a normal prothrombin time by Mephyton has the disadvantage that the patient becomes refractory to anticoagulants for several days There are 5 mg oral tablets of Mephyton

Contraindications to Anticoagulants Anticoagulants are contraindicated in patients with significant hepatic renal or hematologic disturbances This refers more specifically to liver disease in which there is impaired formation or storage of fibrinogen vitamin K etc renal insufficiency which may exaggerate the

concentration of anticoagulant or hematologic disturbances associated with a bleeding tendency. Anticoagulants should not be given if there is uncertainty as to the differential diagnosis between acute myocardial infarction and dissecting aneurysm of the aorta. They are contraindicated in the presence of active bacterial endocarditis, ulcerations and open wounds, recent surgical operations on the brain or spinal cord, postoperative tube drainage of wounds or viscera, or recent ulceration of and bleeding from the gastrointestinal tract.

Administration of Anticoagulants. Heparin, repository heparin, Dicumarol, Tromexan and phenylindanedione are the anticoagulants most commonly employed, but a number of newer preparations have been used recently and will be discussed.

In practice, blood is drawn for determination of the Lee White coagulation time and for a prothrombin time and if these are normal 200 to 400 mg. of Depo-Heparin (repository form of heparin by Upjohn) is injected intramuscularly. At the same time I administer orally 1500 to 1800 mg. of Tromexan and either 300 mg. of Dicumarol or 200 to 300 mg. of phenylindanedione (marketed as Hedulin or Danilone). The heparin is designed to give an immediate anticoagulant effect lasting at least 24 hours. The Tromexan acts most rapidly of the oral anticoagulants and prolongs the prothrombin time adequately by the end of 24 hours. Finally the phenylindanedione or Dicumarol becomes effective by the end of 48 hours, the former usually earlier than the latter. Since therapy is to be continued with either the indanedione or the Dicumarol, 100 mg. of the former or 150 to 200 mg. of the Dicumarol is ordered the second day. A second dose of Depo-Heparin (200 mg.) may be given after 12 or 24 hours if the coagulation time is inadequately prolonged and if the Tromexan has not yet prolonged the prothrombin time satisfactorily. Tromexan is not repeated. After 48 hours therapy is continued with the indanedione (Hedulin or Danilone) or Dicumarol. The oral anticoagulants are given in such dosage as to maintain the prothrombin time at 2 to 2½ times the control value. When the *control time*, as determined by the one stage Quick or Link Shapiro method on a normal subject not receiving anticoagulants is 12 to 13 seconds, the induced prothrombin time in the patient should range between 25 and 35 seconds. This corresponds to a prothrombin *concentration* of about 10 to 30 per cent of normal, when determined by serial dilution of plasma. However, normal, pathologic and anticoagulant treated plasmas cannot be compared accurately by this method of serial dilution. If the prothrombin time is also determined on 12.5 per cent plasma, the prothrombin time should be prolonged two to four times that of the control, e.g., to 70–140 seconds when the control is 35 seconds. It should be noted also that while heparin is being used this drug will prolong the prothrombin as well as the coagulation time. The administration of anticoagulants is continued for at least three weeks, the period of highest incidence of thromboembolism, and until the patient is ambulant. Long term anticoagulant therapy is discussed below.

Individual Anticoagulants[9, 24, 30, 148] HEPARIN SODIUM. Heparin may be injected intravenously or intramuscularly. The dosage is adjusted to prolong and maintain the coagulation time to between 30 and 60 minutes in contrast to a normal coagulation time of 9 to 15 minutes by the Lee-White method. About 300 mg. is administered in 24 hours with some variation according to the age and weight of the patient. It may be administered in a slow, continuous intravenous infusion of 5 per cent glucose in distilled water, containing the 300 mg. of heparin sodium in a liter of fluid. It may also be administered by intermittent intravenous injection in 50 mg. doses every 4 to 6 hours or a concentrated *aqueous solution* of heparin may be administered intramuscularly in 100 mg. doses every 8 hours.

REPOSITORY HEPARIN (Lederle) OR DEPO-HEPARIN (Upjohn). These are long acting preparations containing 200 mg. per cubic centimeter in an aqueous menstruum containing 16 or 18 per cent gelatin and 7.5 or 8 per cent dextrose and are generally preferred to heparin sodium because only one or two injections are necessary in 24 hours. Two hundred to 400 mg. are injected deep intramuscularly at the onset and 200 mg. may be repeated after 12 to 24 hours according to the coagulation time.

The heparin should not be administered in patients with hemorrhagic diseases, or recent active gastrointestinal ulceration or when the coagulation time is prolonged 60 minutes by the Lee-White method. Excessive heparin

effect may be neutralized by the slow intravenous administration of *50 to 200 mg of protamine sulfate* (Lilly) Transfusion of blood may be necessary rarely if there is excessive bleeding

DICUMAROL (bishydroxycoumarin) is a coumarin preparation which was introduced early and is still widely used although some of the newer anticoagulants appear preferable The initial dose is 300 mg But only 200 mg is given to patients with right sided congestive heart failure or small individuals Correspondingly 200 mg or 100 mg respectively is given the following morning Thereafter 50 to 150 mg is given daily, preferably in divided doses according to the prothrombin time Most patients require 50 to 100 mg after the desired prothrombin level is attained Smaller doses may suffice in patients with hepatic or renal disease or congestive heart failure Satisfactory anticoagulation is usually attained with Dicumarol in 48 to 72 hours and its action persists for 3 to 8 days after the drug is discontinued Mild diarrhea headache and rash have been encountered occasionally If the prothrombin time is prolonged excessively (more than three to four times the control time) or if bleeding occurs Dicumarol is temporarily discontinued and if necessary vitamin K_1 (Mephyton) is administered (p 575)

TROMEXAN[111, 138] (ethyl biscoumacetate—Geigy) is also a coumarin derivative which possesses the advantage over Dicumarol of a more rapid onset of effective action usually in 18 to 36 hours and more rapid dissipation of action 36 to 72 hours after it is discontinued However the drug is relatively expensive and in my experience provides less constant control of the prothrombin time I usually employ a single dose of 1500 to 1800 mg at the onset at the same time that some other preferred but slower acting anticoagulant is administered However when Tromexan is used continuously the average daily maintenance dose is 300 to 900 mg in divided doses after the desired prothrombin time is attained

PHENYLINDANEDIONE[133, 31] (Hedulin—Walker or Danilone—Schieffelin) available in 50 mg tablets is not a coumarin derivative It possesses the advantage of a more rapid onset of effective action than Dicumarol in 24 to 36 hours Its activity is dissipated in 2 to 4 days The initial dose is 200 mg and 100 mg is given the following morning When a satisfactory prolongation of the prothrombin time is attained the maintenance dose is 25 to 50 mg *twice* daily

DIPHENADIONE (Dipaxin—Upjohn)[64, 103, 44] This is a new prothrombinopenic oral anticoagulant of the indanedione group namely 2-diphenylacetyl 1 3 indanedione With an initial dose of 30 mg therapeutic anticoagulant effect is attained in about 40 hours according to Katz et al, but a longer period was reported by other observers using a dose of 25 mg[103] The effect persists between 6 and 10 days but this can be abbreviated by vitamin K_1 Its chief merit appears to rest on the claim that the daily maintenance dose fluctuates little in the same or different individuals, and averages 3 to 5 mg Katz and associates[44] have employed an initial combination of 1500 mg of Tromexan with 30 mg of Dipaxin and continued with maintenance doses of Dipaxin alone In this manner the advantage of early anticoagulant effect of Tromexan could be attained without its disadvantages with prolonged use According to Field and associates [illegible] Dipaxin is especially useful for long term maintenance therapy of patients with thromboembolic diseases since prothrombin determinations may be necessary only at intervals of two or more weeks Field et al[44] gave an initial dose of 20 to 30 mg followed by 10 to 15 mg the second day Then maintenance therapy was continued according to the individual's response

CUMOPYRAN[109, 8] (Cyclocumarol—Abbott) (Methopyranorin or 4 hydroxycoumarin) is another coumarin derivative which produces satisfactory prolongation of prothrombin time in 36 to 48 hours but its action persists even longer than that of Dicumarol 12 to 14 days after discontinuation The initial dose is 150 mg and the maintenance dose 12 5 to 50 mg daily Control of prothrombin time is more difficult than with the other preparations mentioned but Brunton et al[25] found that cumopyran produced a constant individual response to a therapeutic dose and that it was one of the best of the 4 hydroxycoumarin group of anticoagulants

MARCUMAR[18, 106] *is a new oral anticoagulant* and like Dicumarol is a 4 hydroxycoumarin derivative [3 (1 phenyl propyl)-4 hydroxycoumarin] Pharmacologically it acts by depressing both the proconvertin and prothrom

bin in the plasma When Marcumar is given in therapeutic doses anticoagulant activity is detected after 24 hours reaches its peak after 48 hours and persists between 4 and 5 days although Prior[106] found that it persisted 9 to 14 days Compared with Dicumarol its activity starts earlier is more prolonged and is twenty times as great per milligram of dose However its onset is somewhat later than that of Tromexan The recommended dosage of Marcumar[8] is 21 mg in a single dose on the first day 9 mg the second day and thereafter a usual maintenance dose of 3 mg daily These doses are modified as necessary in order to maintain the undiluted prothrombin time between 20 and 35 seconds (control 15 seconds) and the diluted prothrombin time between 70 and 160 seconds (control 38 seconds) Excessive reduction in prothrombin time may be controlled by vitamin K_1 (p 575)

Table 9 Oral Anticoagulants Time of Action and Dosage*

ANTICOAGULANT	ONSET OF THERAPEUTIC LEVEL HRS	PERSISTENCE OF ACTION AFTER DISCONTINUATION DAYS	INITIAL DOSE (FOLLOWING DAY GIVE ½ TO ⅔) MG	MAINTENANCE DOSE AFTER THERAPEUT LEVEL MG
Dicumarol	48 72	4 7	200 300	50–150
Tromexan	18 36	1½ 3	1500–1800	300–900
Phenindanedione (Hedulin Danilone)	24–48	2–4	150 200	[illegible] 100
D phenadione (Dipaxin)	24–72	more than 7	30	3 5
Cumopyran (Cyclocumarol)	36–48	12 14	150	12 5 to 50
Marcumar	24 48	4 5 (9 14)	21 (9 mg 2nd day)	3
Warfarin (Coumadin)	18 36	5–7	50 75	5 25 mg at 1–3 day intervals
Sinthrom (Acenocoumarin)	24–48	2	20	4 6

* Dosage is approximate and must be controlled by determination of prothrombin time and careful observation of the patient for evidence of bleeding

WARFARIN (Coumadin sodium—Endo) is a synthetic anticoagulant with the chemical name 3 (α acetonylbenzyl) 4 hydroxycoumarin Warfarin sodium administered orally or intravenously produces therapeutic hypoprothrombinemia in appropriate dosage[243, 105] By both routes a therapeutic range is usually achieved within 24 (16 to 36) hours and is maintained for 5 to 7 days The intravenous route is indicated only when oral medication cannot be tolerated The initial dose of the intravenous or oral medication is 1 mg per kilogram of body weight but rarely exceeds a maximum of 75 mg Subsequent dosage based on prothrombin time determination is given when the peak effect is achieved usually on the third or fourth day The next dose is approximately two thirds the initial dose Maintenance dosage of 12 5 mg or 25 mg is given daily or every other day occasionally every third day according to the prothrombin time and whether it is rising or falling According to Pollock[105] the maintenance dose is 5 to 20 mg daily, average 10 mg The prothrombin *concentration* should be 10 to 30 per cent (usually 25 to 35 sec prothrombin time with control of 12 sec)

Warfarin possesses the advantage of rapid therapeutic effect similar to that of Tromexan but its action is more prolonged and it is easier to control the hypoprothrombinemia at stable levels

SINTHROM (Acenocoumarin—Geigy) a new 4 hydroxycoumarin oral anticoagulant is effective in small doses and is reported to be quite satisfactory with respect to ease of controlling the prothrombin time and relative safety[120] The initial dose is 20 mg followed by 8 to 16 mg on the second day The maintenance dose is 4 to 6 mg daily In 85 per cent of the patients, the therapeutic range of prothrombin time was attained in 48 hours or less The prothrombin time approached normal 30 hours after the drug was discontinued[141a]

Long Term Anticoagulant Therapy [1, 97, 6, 135] The prolonged administration of anticoagulants is now being recommended to prevent further attacks of acute myocardial infarction Favorable results have been reported by Nichol et al [97] in a series of 295 patients treated from three months to seven years and by Tulloch and Wright[134] in 227 patients Such therapy is employed chiefly in those patients who have suffered recurrent myocardial infarction especially when complicated by other evidences of thromboembolism This is obviously a project which will require a long period of time to evaluate and one in which it will be difficult to prove the efficacy of the procedure because of the absence of control and of matching cases and the variable outlook in reported series of cases of coronary thrombosis However Suzman et al [136] treated 82 patients with anticoagulants for 3 to 76 months following myocardial infarction whereas a group of 88 patients who had received anticoagulants only during the acute attack served as controls The mortality rate was 7 3 per cent in the group receiving long term treatment and there were 7 recurrences of myocardial infarction In the control group the mortality rate was 33 per cent and there were 24 recurrences Favorable effects of long term anticoagulant therapy were also reported by Keyes et al [65] by Manchester [91] and by Murr [96]

During the course of long term therapy repeated determination of the prothrombin time is essential but in most patients the prothrombin times and anticoagulant dosage become sufficiently stabilized to permit intervals of one two or occasionally three weeks between determinations Hemorrhagic complications are more frequent in patients on long term anticoagulant therapy than in those receiving such treatment only during an acute myocardial infarction Hematuria hematoma or ecchymoses occur most commonly But melena epistaxis menorrhagia hematemesis hemoptysis and other forms of hemorrhage have also been noted As a rule these can be controlled by temporary discontinuance of the drug and by the administration of vitamin K_1 (Mephyton)

Sedatives and Soporifics Sedatives are among the most widely used and most valuable drugs in the treatment of cardiac infarction They are employed after subsidence of severe pain eliminates the need for morphine or similar opiates In certain cases with little or very transient pain, sedatives and soporifics may be the only drugs required *Phenobarbital* in doses of 15 or 30 mg (¼ or ½ grain) three times daily is commonly given to allay apprehension anxiety or restlessness and often causes mild drowsiness It may also reduce the susceptibility to ectopic rhythms especially ventricular tachycardia It is often advisable to maintain the patient in a somewhat drowsy state during the first days of the acute illness Phenobarbital may have to be supplemented by soporifics such as Seconal 0 1 gm (1½ grains) Nembutal (pentobarbital) 0 1 gm (1½ grains) barbital 0 3 gm (5 grains) Ipral calcium 0 12 gm (2 grains) Sedatives and soporifics should not be given to the point of causing respiratory or mental depression In some patients the barbiturates cause excitement instead of depression especially with large doses Continued use may cause a dermatitis in susceptible individuals

Bromides 1 gm (15 grains) or chloral hydrate 0 3 to 0 6 gm (5 to 10 grams) alone or in combination with bromides may be substituted or alternated with the phenobarbital During the period of recovery Demerol for occasional or persistent moderate pain or codeine for milder pain administered orally or hypodermically may be combined with sedation

Digitalis Digitalis should be employed in the treatment of acute myocardial infarction only when there is congestive heart failure or an arrhythmia with very rapid ventricular rate While there is general agreement as to the indication for digitalis whenever heart failure develops many physicians avoid it when the heart failure is associated with acute myocardial infarction Following is an evaluation of the objections mostly theoretical which have been raised to the use of digitalis in acute myocardial infarction

1 By increasing the force of cardiac contraction digitalis it is argued may rupture the weak infarcted muscle or dislodge a mural thrombus This purported danger implies that digitalis increases the intraventricular pressure Neither congestive heart failure nor digitalis has a consistent effect on the systolic blood pressure On the contrary an increased diastolic pressure is produced not by digitalis but by cardiac failure

2 Because the ischemic myocardium is

hyperirritable following acute coronary occlusion, it is feared that digitalis may increase this irritability and promote the probability of ventricular tachycardia and ventricular fibrillation While digitalis has been known to cause extrasystoles it has also diminished or abolished them No justifiable conclusion can therefore be drawn that digitalis will cause this serious arrhythmia when given in therapeutic doses to humans The basic reason for serious arrhythmias after coronary occlusion is the consequent myocardial anoxia, since digitalis improves the metabolic efficiency of the failing heart muscle, it may diminish rather than increase their frequency Askey[2] found no evidence of an increase in ventricular ectopic rhythms in a group of 50 patients with proved myocardial infarction who were given digitalis in therapeutic dosage as compared with a control group who were not treated with digitalis

3 It is feared that digitalis may further diminish the already depressed cardiac output which is associated with cardiac infarction and shock But although digitalis reduces the cardiac output in health it increases the cardiac output when heart failure is present (p 250)

4 Another objection to the use of digitalis after acute coronary occlusion is the belief that digitalis causes constriction of the coronary arteries But the available experimental and clinical evidence is contradictory as regards this contention

In the absence of more convincing objections it has been my practice to administer digitalis for the treatment of heart failure after myocardial infarction unless the heart failure is readily controlled by the more immediate measures of bed rest opiates oxygen therapy and occasionally venesection If there is gross right and left sided heart failure digitalis is administered whenever these manifestations appear But in the presence of very mild left sided failure alone digitalis is usually not administered until a week after onset when the acute features of the disease have disappeared or become stabilized When heart failure is characterized by acute pulmonary edema which does not respond to other emergency measures strophanthin may be given in the form of ouabain beginning with 0 25 mg intravenously and repeated in an hour if necessary An additional 0 25 to 0 50 mg may be given intravenously or intramuscularly 12 hours later This drug should not be given if the patient has been receiving digitalis immediately prior to the attack Other digitalis preparations for intravenous digitalization have been discussed (p 262), e g Cedilanid, 4 cc intravenously, if there is no immediate emergency [illegible]

For less severe left ventricular failure characterized by persistent dyspnea or paroxysmal dyspnea, as well as for the fully developed symptoms and signs of right- and left sided heart failure with or without sinus rhythm, the patient should be digitalized in the manner previously outlined (p 259) As always, the most important guide to digitalis dosage is the clinical response of the individual patient

Rales at the extreme bases of the lungs posteriorly are commonly present from the outset of acute myocardial infarction, but in themselves are insufficient indication for the use of digitalis or diuretics in the first days of illness They do not necessarily represent fluid retention, but rather indicate a redistribution of blood to the pulmonary circulation due to the acute injury to the left ventricle They usually disappear spontaneously before the end of the first week

Mercurial Diuretics These preparations (p 271) are indicated chiefly in cases of acute cardiac infarction which are characterized by right and left sided congestive heart failure from the very beginning, and in cases in which congestive heart failure becomes manifest after the patient resumes activity They are less widely used, but are also of striking benefit for the treatment of recurrent nocturnal paroxysms of cardiac asthma which may develop early after cardiac infarction Like digitalis mercurial diuretics are not administered early unless there is gross, right sided heart failure or persistent pulmonary edema After a week a mercurial may be given if there are persistent symptoms and signs of left- or right-sided heart failure

Quinidine Quinidine is employed during the treatment of acute cardiac infarction to combat the development of numerous and troublesome premature contractions, persistent atrial flutter and fibrillation without cardiac failure and ventricular tachycardia (see below) There is no significant basis to justify its routine use for the purpose of preventing these arrhythmias [illegible]

Antibiotics These drugs are frequently used

in the treatment of acute myocardial infarction either because there is a definite complicating pneumonia or because it is sometimes difficult to distinguish between extensive pulmonary congestion (especially when complicated by infarcts) and bronchopneumonia. Roentgenologic examination is not always feasible and does not easily distinguish between pulmonary infarction and pneumonia. In general it is preferable to administer penicillin in the form of crystalline procaine penicillin in an average single daily intramuscular dose of 300,000 units. Or else penicillin 400,000 units and streptomycin 1 gm. are administered in combination or a broad spectrum antibiotic such as tetracycline 250 mg. four times daily is administered orally. Some physicians routinely prescribe antibiotics as a prophylactic if there is evidence of pulmonary congestion (moist rales at the bases) and fever.

Insulin. The question of the use of insulin arises frequently because cardiac infarction is common in diabetics and because the risk of hypoglycemic shock is especially great for the ischemic myocardium. Hyperglycemia and mild transient glycosuria are fairly common after acute coronary occlusion; in themselves they are no indication for the use of insulin and they may not denote any more than potential diabetes (p. 520). On the other hand, insulin should be used in patients with uncontrolled diabetes, which is often intensified by the occlusion, but the dosage should be such as to permit a mild glycosuria or at least a moderately elevated blood sugar as a margin of safety. In my experience in such cases regular insulin administered as needed according to the findings in fractional specimens is preferable to and safer than routine orders of protamine zinc insulin.

Corticosteroids. The problem of administering cortisone or other adrenocorticosteroids for associated disease sometimes arises during the course of an acute myocardial infarction. On the one hand, it is theoretically possible that the inhibition of inflammatory reaction might beneficially permit better penetration of the infarct by collateral vessels; on the other hand, inhibition of healing might predispose to cardiac rupture or imperfect scar formation. Johnson and associates[61] reported that cortisone administration begun at the time of experimental ligation of a coronary artery in dogs resulted in strikingly smaller infarcts and other benefits as compared with the findings in operated dogs which did not receive cortisone. However, such benefits were not observed in similar studies by others.[33, 62] In fact, there was usually a slight inhibition of the rate of removal of necrotic muscle with consequent delay in healing. Clinical observations have not been decisive in my experience, but it appears preferable to interrupt the administration of cortisone, unless absolutely essential, at least during the first three weeks after an acute myocardial infarction.

Other Drugs. Atropine is not used for the treatment of acute myocardial infarction but may be employed if there is heart block without Adams-Stokes syndrome.

Neither are the xanthine drugs employed any longer except that *aminophylline* is given intravenously or as a rectal suppository for the control of Cheyne-Stokes respiration and for the control of paroxysmal dyspnea or cardiac asthma.

Papaverine has not been found to be beneficial for the myocardial infarct. It has been used occasionally intravenously (0.1 to 0.2 gm.) to relieve arterial spasm at the onset of peripheral embolization.

Nitrites are not employed in the treatment of acute myocardial infarction and are regarded as potentially dangerous because they may induce a fall in blood pressure. However, many patients who have been taking nitrites for preceding episodes of angina pectoris often take them at the onset of acute myocardial infarction. Often it is the failure of the nitrites to relieve pain which leads the patient to summon his physician, or which indicates to the physician that he is dealing with a case of acute myocardial infarction and not angina pectoris.

The intravenous injection of trypsin was claimed to dissolve experimentally induced coronary thrombi[1] and to have a beneficial anti-inflammation effect in human cases of thromboembolism including coronary thrombosis.[62] Studies by Taylor and Wright[131] failed to provide evidence to justify the use of parenteral trypsin as a therapeutic agent in man.

TREATMENT OF COMPLICATIONS

The management of cardiac shock (p. 562), acute pulmonary edema (p. 566) and other forms of congestive heart failure has been

discussed above as the treatment of intrinsic manifestations of acute cardiac infarction rather than of complications

Arrhythmias

Premature beats, usually ventricular are common, rarely affect the prognosis, or require treatment However, when ventricular premature beats recur frequently and cause subjective annoyance Pronestyl (p 340) or quinidine may be administered (p 341)

Ventricular Tachycardia Pronestyl and quinidine are the drugs of choice in its treatment, but potassium and magnesium salts and other drugs have been recommended (p 374)

Atrial Fibrillation Usually paroxysms of atrial fibrillation in the course of cardiac infarction subside spontaneously after several hours and thereafter require no treatment When persistent, quinidine may be given in an effort to restore regular rhythm (p 365) When atrial fibrillation is associated with congestive heart failure or a high ventricular rate, digitalis should be given according to the principles previously outlined (p 259) Subsequently digitalis may be stopped temporarily and quinidine administered in an effort to restore sinus rhythm

Embolism

Since *pulmonary embolism* arises almost exclusively from venous thrombi in the lower extremities, prevention of such thrombosis is more important than efforts at treatment after embolization occurs This is accomplished by early leg exercises and early ambulation, e g to the lavatory

Embolization of a Peripheral Artery Embolectomy is the most important single therapeutic measure and promises restoration of circulation in a high percentage of cases if the operation can be performed within 12 hours after the occurrence of the embolism [65, 128, 141] The results of embolectomy are rarely satisfactory, even as regards the restoration of circulation, if more than 24 hours have elapsed However, Atlas[4] reported recovery of a patient operated upon successfully for an aortic embolus 60 hours after its occurrence As a rule, embolectomy is indicated when the embolus is situated at the bifurcation of the aorta, of the common iliac artery or of the femoral artery But embolectomy is only occasionally or rarely necessary for embolization of the upper extremity or of the popliteal or more distal arterial branches of the lower extremity, because there is an adequate collateral circulation In the latter instances an attempt at surgical removal of the embolus should be performed only if there is loss of function of the muscles supplied by the affected artery, or progressive changes

Although the ultimate outlook for patients with embolization is poor, with or without embolectomy, because of the serious underlying cardiac disease, many lives and more extremities could undoubtedly be salvaged by embolectomy Griffiths[54] found that 87 per cent of patients with arterial embolism who were not operated upon died within a fortnight and the remainder required a major amputation On the other hand Key[65] reported successful embolectomies in 216 cases Even in cases of saddle embolus of the aorta, which is almost invariably fatal, recoveries have been reported following embolectomy [78, 141, 119a]

The immediate treatment of peripheral arterial embolism includes the administration of opiates for the severe pain that is usually present The ingestion of alcoholic beverage may also be helpful, because of both its analgesic and antispasmodic action When the lower extremity is involved the head of the bed should be elevated or the legs should be hung down over the side of the bed periodically The application of heat is dangerous and should be avoided But the room should be kept warm and a cradle with one or two electric light bulbs may be placed over the extremity Warm packs may be applied to the unaffected extremities Papaverine (60 to 120 mg) or tolazoline (Priscoline) (25 to 50 mg) may be administered intravenously or intra arterially proximal to the occlusion If effective, this can be repeated if local circulatory insufficiency recurs Paravertebral lumbar sympathetic block with procaine or alcohol may be beneficial if these measures fail This procedure is designed to relieve associated arterial spasm and thus improve the collateral circulation But it is probably safer to avoid paravertebral block if anticoagulants are to be administered, as they should be The Sanders oscillating bed may be employed with the maximal low foot and minimal low head adjustment

Anticoagulants should be administered as soon as possible Heparin in doses of 50 mg should be administered intravenously every 4 hours and oral anticoagulants should be

started as described on page 576 If these various measures are ineffective within 4 to 6 hours embolectomy should be performed[17] This is most often necessary for embolism of the abdominal aorta or common iliac artery If the surgeon desires the effect of the heparin may be neutralized preoperatively by the administration of protamine sulfate intravenously But anticoagulant therapy should be instituted postoperatively If it is too late for embolectomy and there is evidence of beginning gangrene refrigeration of the extremity may be tried With the development of gangrene amputation is usually necessary

Diabetic Acidosis

Although diabetic acidosis and coma complicating acute cardiac infarction may be difficult to control because of the active cardiac process the general principles of controlling diabetic acidosis should be followed Parenteral fluids and insulin should be administered promptly and in sufficient amounts to control hyperacetonemia dehydration and shock The danger of hypoglycemic shock must be avoided and if the acidosis is controlled insulin should not be pressed to the point of completely abolishing glycosuria and hyperglycemia One should also avoid the danger of precipitating pulmonary edema by giving excessive quantities of fluid especially fluids containing sodium The necessity of hospitalizing patients with acute myocardial infarction and diabetic coma for continuous observation and frequent physical and laboratory examinations appears obvious

Periarthritis of Shoulder and Disturbances of Hand

Pain and disability of the shoulder and arm and trophic disturbances of the hand usually run a protracted course and are resistant to treatment As a rule the shoulder arm symptoms subside spontaneously after three to twelve months or longer depending on their severity Procaine infiltration of local trigger zones and various physiotherapeutic and orthopedic measures have been employed with uncertain effect Prednisone (Meticorten) in doses of 20 to 60 mg daily is often effective Roentgen ray therapy has frequently afforded relief when all other measures failed Relief has also been reported following the local injection of 50 mg of hydrocortisone into local trigger areas[12] Adequate analgesics or even occasional opiates are required for relief of pain and should be administered Motion should be encouraged as tolerated but not to the point of pain active manipulation should be avoided Stellate ganglionectomy upper dorsal sympathetic blocks with procaine or surgical dorsal sympathectomy has been recommended by Steinbrocker and his associates[17]

Aneurysm of the Ventricle

Excision of a ventricular aneurysm (ventriculoplasty) has been recommended because of the frequent association of intractable heart failure persistent angina pectoris and arterial emboli[74] This is still in the realm of research

Rupture of Ventricular Wall or Interventricular Septum

Whenever the diagnosis of perforation of the interventricular septum is made in the course of acute myocardial infarction the defect should be repaired as soon as shock can be controlled If cardiac rupture is suspected a pericardial aspiration should be performed If blood is obtained the patient should be typed and suitable blood should be made available for transfusion if necessary If rupture of the ventricle is indicated by recurrent tamponade despite aspiration a thoracotomy should be performed and the ventricular rupture repaired

Sudden Death

It seems paradoxical to discuss the treatment of sudden death in myocardial infarction yet often the immediate cause of death and death itself are not irreversible if treatment is instituted promptly When death is due to a disturbance in cardiac mechanism usually ventricular fibrillation or cardiac standstill it is possible to restore the normal cardiac mechanism as described under cardiac arrest (p 1109) without recurrence of the cardiac arrest Thus Beck et al[10] described the case of a physician who died from an acute myocardial infarction while leaving the hospital A thoracotomy was performed and cardiac massage instituted within three minutes Ventricular fibrillation was observed and sinus rhythm was restored by electric shock applied to the heart The patient recovered A similar case was reported by Reagan et al[106]

CONVALESCENCE AND REHABILITATION

The duration of convalescence and the decision as to whether and when a gainful occupation may be resumed must be determined individually in each case Patients with pro

nounced and persistent symptoms of congestive heart failure, with angina pectoris recurring frequently at rest or after minimal effort or with extreme weakness may require an indefinitely prolonged period of convalescence It is often necessary to adjust the patient to the necessity of indefinite or permanent retirement from work or business and psychotherapy becomes a dominant element in medical management

The physician should not enforce prolonged invalidism merely because the patient has experienced a severe attack Nor should the patient be led to believe that chronic invalidism is the inexorable consequence of myocardial infarction even if the symptoms do not permit a complete restoration of previous activity The physician must assess the comparative merits of a miserable enforced invalidism, of which the effect on longevity is questionable against a less confined but happier life which may involve slight theoretical risks

Patients who recover from the acute attack and who experience little or no distress as they become ambulant should nevertheless spend a variable period after recovery in gradually resuming normal care of themselves in the home and short walks outdoors When this is accomplished a holiday of two weeks or longer is often desirable to induce a philosophic and psychologic readjustment

The resumption of physical exertion after convalescence often presents a problem Many patients complain of weakness and experience dyspnea on moderate exertion Careful *evaluation is necessary to determine* whether these symptoms are the consequence of extensive myocardial infarction and congestive heart failure if so, limitation of physical exertion must be continued and treatment designed to improve the cardiac and circulatory status On the other hand, these symptoms are often the consequence of inactivity poor muscular tone and other related disturbances which go under the heading of lack of training Under these circumstances fatigability weakness and dyspnea on exertion may be best managed by graduated exercises and the gradual resumption of muscular activity At least a fair trial should be made to determine whether the response to such a graduated regimen is favorable or not Sometimes fear and anxiety associated with the knowledge of having suffered a heart attack leads to an almost neurotic timidity of any physical effort The need for reassurance and explanatory discussions is obvious

An increasing number of patients have come to my attention with complaints of weakness and disability which are attributed to persistent residuals of acute myocardial infarction, but which are found to be manifestations of a reactive depression Despite some risk in the procedure, electric narcosis therapy has been administered to many such patients with excellent results Others have benefited from the use of reserpine and/or chlorpromazine (Thorazine) in large doses

About one third of the patients are well enough to return to their previous work and engage in all their normal activities Although "moderation in all things" should be recommended, no long list of restrictions is justified [74] There is no objection to climbing a flight or two of stairs if this can be done without distress i e, if there is no angina pectoris or heart failure Sexual relations may be resumed if there are no distressing symptoms Nitroglycerin may be taken prophylactically if sexual activity results in angina pectoris Walking golf fishing riding and swimming are permissible in the absence of heart failure and angina pectoris Similarly air travel is permissible but above 8000 feet flying must be done in properly pressurized cabins [illegible] Flying should be avoided if heart failure is *present and for at least two months after an* acute myocardial infarction I uniformly recommend that smoking be discontinued

Economic as well as medical considerations *often dictate the extent to which the patient* can modify his type of work, the conditions and hours of his employment, periods of rest and vacations In some instances through the *effort of individuals in others through* the work of various local heart associations the cooperation of employers has been enlisted in finding suitable work for patients who have suffered an acute cardiac infarct These activities should be broadened and extended In many cities there are now *cardiac work classification units* in which a coordinated effort by cardiologist, psychiatrist social worker and other professional workers serves to determine the patient's capacity for work to help in his rehabilitation and to aid in finding suitable employment [illegible, 36a]

Self-employed business and professional men should be persuaded to obtain an assistant or to delegate more and more of the less

important and especially the more strenuous and time consuming duties to other associates. The objective should be the elimination of severe physical exertions of prolonged hours of work of emotional tensions of excessive duties of the pressure of dead lines or of work which does not permit reasonable and regular hours for meals relaxation and vacations

For those patients who are compelled or prefer to retire completely from work some program should be formulated to avoid ennui if not actual depression The resumption of an old hobby or the development of a new one is particularly desirable This often provides a test for the physician s initiative ingenuity persuasiveness and enthusiasm Television and the movies are often sought to fill the days and evenings Considerable discretion and censorship may be necessary to choose programs which amuse and relax and do not bore or excite Card playing may be a pleasurable form of diversion but in general play for stakes of any kind should be prohibited Patients who become too excited even when no stakes are involved should not play at all

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PART V

STRUCTURAL ABNORMALITIES OF THE HEART

Chapter 22

ACUTE PERICARDITIS

Pericarditis is an inflammation of the enveloping membranes of the heart, i.e., the visceral or parietal pericardium or both. It is almost always a part of, secondary to, or a complication of some other disease. It may be the result of a bacterial infection or a manifestation of some general disease such as rheumatic fever. Pericarditis may represent the sole cardiac lesion or it may develop in combination with myocarditis, endocarditis or both. Diagnostically, the term pericarditis is itself incomplete; whenever possible the etiologic agent or disease should be determined and expressed.

The *incidence of pericarditis* of all types based on necropsies has been given as between 4 and 12 per cent[11] and that of acute pericarditis between 3 and 7 per cent[10] of all autopsies. The incidence of pericarditis as determined clinically is much lower for some cases produce no significant symptoms and a great many with symptoms are undiagnosed.

CLASSIFICATION AND ETIOLOGY

Pericarditis may be classified etiologically according to the causative bacterial agent when known, or according to the disease of which it is a part or a complication. The following etiologic varieties of pericarditis have been noted:

1. Rheumatic pericarditis
2. Uremic pericarditis
3. Bacterial pericarditis (pneumococcus, streptococcus, staphylococcus, etc.)
4. Tuberculous pericarditis
5. Acute nonspecific pericarditis
6. Pericarditis secondary to myocardial infarction. Pericarditis in periarteritis nodosa
7. Pericarditis due to malignant neoplasm
8. Traumatic (usually bacterial) pericarditis
9. Pericarditis following mitral commissurotomy
10. Pericarditis of Libman-Sacks disease (lupus erythematosus)
11. Syphilitic (gummatous) pericarditis
12. Actinomycotic pericarditis
13. Pericarditis associated with parasitic disease, especially echinococcus and cysticercus
14. Other forms. Goldman and Lau[41] reported 2 cases of acute pericarditis in association with serum sickness following tetanus antitoxin.

The records of 96 cases of acute pericarditis diagnosed in a general hospital in 16 years[41] showed that rheumatic fever was responsible for 40.6 per cent, bacterial infection for 19.8 per cent, tuberculosis for 7.3 per cent, benign non specific pericarditis was present in 10.4 per cent, uremia in 11.5 per cent, neoplasm in 3.1 per cent and so-called "collagen disease" in 2.1 per cent. Males predominate over females in cases of acute pericarditis.

PATHOLOGY

Pericarditis has been classified pathologically according to the type of pericardial reaction and exudate. The following are the most common forms: fibrinous pericarditis, serofibrinous pericarditis, hemorrhagic pericarditis, purulent or suppurative pericarditis and adhesive pericarditis. Combinations of the above are not infrequent. Pericarditis has been classified also into certain clinical pathologic groups usually: (1) acute fibrinous pericarditis, (2) pericarditis with effusion, (3) chronic adhesive pericarditis, (4) constrictive pericarditis.

Hemorrhagic pericarditis is a variant of serofibrinous pericarditis in which the effusion contains sufficient blood to give it a grossly hemorrhagic appearance. It occurs

most commonly in neoplastic, lymphomatous and tuberculous pericarditis but may occur in other chronic types Hemorrhagic pericarditis is to be distinguished from hemopericardium (p 604)

Chylopericardium is characterized by a milky pericardial effusion due to obstruction of the thoracic duct by neoplasm[118] or as a result of trauma[3]

Cholesterol pericarditis in which the effusion is rich in cholesterol has been reported[89] In Alexander's case the fluid had the appearance of gold paint Cholesterol pericarditis is usually associated with myxedema, but may occur with hemopericardium or tuberculous pericarditis A case of chronic constrictive cholesterol pericarditis was successfully treated by pericardiectomy

CLINICAL FEATURES

SUBJECTIVE SYMPTOMS

There are three groups of symptoms (1) pain or precordial distress (2) dyspnea and other symptoms resulting from compression of the heart and adjacent thoracic structures and (3) general symptoms due to the pericardial inflammation or to the general disease of which the pericarditis is a part

1 Pain

Precordial pain has long been considered a characteristic symptom of acute pericarditis, but it is probably absent as often as it is present When pain occurs it may be sharp and severe or dull and vague It is usually situated over the precordium but it may radiate to the left shoulder neck and arm to the epigastrium and to the left scapular region and thus simulate the pain of coronary occlusion When the pain is exclusively abdominal, an acute abdominal complication may be erroneously diagnosed the thoracic origin of the pain being entirely overlooked The pain is often intensified by deep inspiration by movement of the chest wall and by cough observations which suggest a relationship to involvement of the costal or diaphragmatic pleura

The *pathogenesis of pain in pericarditis* has been greatly clarified by Sutton and Lueth[85] Capps[19] and others[2] The visceral pericardium is entirely insensitive to pain Pain fibers from the phrenic nerve present only in the lower part of the parietal pericardium may account for pain referred to the left side of the neck The following mechanisms appear to be concerned in the pain associated with pericarditis[19]

(a) Pericardial effusion may produce a dull oppressive pain (protopathic pain) by distention of the entire pericardial sac and therefore of the pain sensitive lower parietal pericardium

(b) An associated (contiguous) pleuritis of the diaphragmatic costal or mediastinal pleura and not the pericarditis, occasions the pain This accounts for the occurrence of sharp pain and for pain with distant radiations outside of the neck

(c) Myocardial ischemia and not an associated pericarditis accounts for pain in cases of coronary thrombosis with myocardial infarction

2 Dyspnea and Other Compression Symptoms

Dyspnea is an early, frequent and usually the most prominent symptom in cases of pericarditis with effusion Objective manifestations are a rapid respiratory rate, shallow and forced respirations and the extreme orthopneic position assumed by the patient

The pathogenesis of the dyspnea is uncertain It is likely that the dyspnea results at least to some extent from actual mechanical compression of the bronchi or lungs and in cases of huge effusions, from the diminished vital capacity caused by encroachment on the available thoracic space This mechanical explanation of dyspnea is consistent with the observation that patients with pericardial effusions are somewhat or moderately relieved by leaning far forward (in contrast to those with pulmonary congestion who merely elevate the head and shoulders) so that the effusion is shifted down from the base of the heart and anteriorly against the chest wall

Occasionally other symptoms besides dyspnea are produced by compression of the trachea bronchi, lungs, and esophagus There may be a dry hacking cough, hoarseness or dysphagia These symptoms are most likely to occur in cases with very large effusions such as are encountered most often with tuberculous pericarditis

3 General Symptoms

General symptoms may be due to the pericardial infection or inflammation as such or to the general disease with which the pericarditis is associated *Fever*, sweating chills, fatigability or weakness loss of weight anxiety de-

pression or delirium may be present, according to the etiology of the pericarditis

OBJECTIVE SIGNS

The objective evidences of acute and subacute pericarditis are (a) changes in physical signs in the chest due to inflammation of the pericardium and the presence of an effusion (b) manifestations of altered circulatory dynamics due to cardiac tamponade or compression caused by elevated intrapericardial pressure and (c) general manifestations of the pericardial inflammation and the associated disease

Physical Signs in the Chest

1 **Pericardial (Friction) Rub** This is a superficial, scraping scratchy or grating sound or occasionally one with a coarse leathery quality There are usually to and fro sounds which phonocardiograms disclose are due to vibrations set up during ventricular and atrial systole and occasionally also during the phase of rapid ventricular filling early in diastole [25]

The pericardial rub is usually heard in the pulmonic area or just to the left of the lower sternum fairly well localized to a small area Its location may shift with a change in the patient's position It is best heard if the patient leans forward and moderate pressure is made on the chest wall with the bell of the stethoscope The pericardial rub is often very evanescent, it may be audible for a few hours at a time and intermittently for a few days, occasionally it persists for weeks or even months Persistent rubs are heard most commonly in pericarditis due to neoplasm but also in uremia, benign pericarditis and occasionally in tuberculous pericarditis

A pericardial rub is usually associated with a dry fibrinous pericarditis However as recognized long ago by Stokes [87] a pericardial rub is often heard also in the presence of a pericardial effusion Conner[23] noted a friction rub in 24 out of 34 cases of pericarditis with effusion While a pericardial rub is a sign of either an acute fibrinous pericarditis or a pericarditis with effusion the following signs are elicited only in the presence of a significant effusion

2 **Increased Width of Cardiac Dullness at the Base of the Heart** The left border of cardiac dullness in the second and third left interspace is significantly shifted to the left This results in a widened area of dullness at these levels especially with the patient in the recumbent position This area of dullness becomes definitely narrower if the patient sits up since the effusion settles lower because of gravity [73]

3 **Generalized Increase in Cardiac Dullness** When there is a considerable pericardial effusion percussion reveals a generalized enlargement of the area of cardiac flatness which assumes a globular shape if the patient is recumbent There may be a characteristic rapid increase or decrease in the area of flatness during the course of the disease There is a sharp transition along the left border from pulmonary resonance to cardiac flatness without the intermediary of relative cardiac dullness

4 **Ewart's or Pins Sign** In cases with large pericardial effusions, there is often a patch of dullness below the angle of the left scapula occasionally extending one third or more of the way over the left lower posterior chest wall Over this dull area there is bronchial breathing and usually also bronchophony or egophony Râles are usually absent although occasionally a few scattered moist rales may be heard While these signs were observed earlier, their significance was stressed first by Pins,[77] the Viennese, and later by Ewart [32] whose name is now attached to this sign in English speaking countries Ewart's sign is due to compression of the base of the left lung by the pericardial effusion which extends posteriorly This explanation has been disputed but in my opinion remains the most plausible

5 **Other Physical Signs** The cardiac impulse is often weak and wavy or may disappear entirely Similarly the heart sounds are usually muffled and distant especially when the patient is recumbent However, I have several times felt a strong apical impulse and heard loud heart sounds in the presence of significant pericardial effusions

There may be a distinct increase in cardiac dullness to the right of the sternum in the fifth intercostal space (Rotch's sign) [85] But percussion is often unreliable in this area and the dullness may be obscured by compensatory emphysema

Cardiac Tamponade

The term cardiac tamponade or acute cardiac compression denotes an interference with the diastolic filling of the heart and with cardiac contraction due to an increase in intrapericardial pressure This occurs in many

cases of pericarditis with effusion, as well as in cases of acute hemopericardium[114]

Hemodynamics of Cardiac Tamponade The following hemodynamic changes in cardiac tamponade have been observed experimentally[94] following the injection of fluids under pressure into the pericardium of dogs,[3, 70] and in clinical studies of human cases of pericardial effusion[111] and hemopericardium[111]

(1) There is a progressive rise in the right intra atrial and venous pressure and in the right ventricular diastolic pressure as the pressure within the pericardium rises (2) There is a reduction in the stroke output and later in the cardiac output per minute as well (3) The cardiac rate increases (4) The arm to tongue circulation time is prolonged (5) The vital capacity diminishes (6) There is a late fall in blood pressure especially in the systolic pressure Since the right ventricular diastolic pressure rises whereas the right ventricular systolic pressure is unchanged or falls slightly, the right ventricular pulse pressure falls

The stroke output diminishes because the elevated pericardial pressure compresses the right atrium and interferes with the venous inflow from the great veins Studies by means of ventricular function curves have disclosed that the major circulatory defect in acute cardiac tamponade is a restriction in diastolic expansion of the ventricles by the pericardial effusion The rise in venous pressure helps to maintain filling but the concomitant rise in atrial pressure diminishes the effective filling pressure difference The rise in venous pressure is a measure of the disparity between the venous return and the ability of the heart to accept and expel that return Venous infusions may increase the venous and right atrial pressure and thereby restore the normal cardiac output or increase it[24, 35]

A normal cardiac output is temporarily maintained by a compensatory tachycardia, probably effected by the elevated venous and right atrial pressure through the Bainbridge reflex The blood pressure is at first maintained by peripheral vasoconstriction But at a critical level of intrapericardial pressure (100 to 150 mm saline) there is a sharp fall in stroke and cardiac output and the blood pressure falls The pulse pressure diminishes because of a greater reduction in the systolic pressure If the intrapericardial pressure is reduced by paracentesis these circulatory abnormalities are reverted more or less toward normal

In clinical pericarditis with effusion, as in the experimental form, the development of cardiac tamponade depends on the rise in intrapericardial pressure, the latter is determined by the quantity of the effusion and its speed of formation A very acute effusion of 150 to 250 cc (in hemopericardium or suppurative pericarditis) can cause tamponade, while slowly developing effusions of a liter or more (tuberculous effusions) may be tolerated if the pericardium is given time to distend and the pressure is only slightly elevated

Clinical Manifestations of Cardiac Tamponade

1 An *acute compression triad* has been stressed by Beck[9] and consists of a rising venous pressure, a falling arterial pressure and a small quiet heart The latter is best observed by fluoroscopy Tachycardia is also a prominent manifestation If the cardiac output is greatly reduced, there is a fall in blood pressure and a clinical picture of shock In cardiac tamponade associated with rapidly formed but relatively small effusions the physical signs of (large) pericardial effusion described above are absent

2 *Systemic venous congestion* occurs with subacute or chronic tamponade due to effusions which develop more slowly In these cases a compensatory increase in circulating blood volume may tend to maintain the cardiac output, but later causes systemic congestion *Engorgement of the cervical veins increased venous pressure* and *enlargement of the liver* are the usual manifestations Compression of the venae cavae may result in increasing cyanosis of the lips face and neck and occasional facial edema If the cardiac output falls sharply during the stage of venous congestion, the clinical picture of shock may be added to that of congestive heart failure

3 *Paradoxical pulse*[89] is an almost constant manifestation of cardiac tamponade There is a *distinct* diminution in pulse amplitude during inspiration This may be revealed more clearly by a fall in blood pressure of 10 to 20 mm Hg or more at the end of inspiration

In the normal person there is a tendency to paradoxical pulse, because the slightly increased venous return during inspiration is more than outweighed by the greater volume of blood accommodated in the chest There-

fore, at full inspiration the cardiac stroke output from the left ventricle and consequently the pulse and blood pressure are diminished In cases of pericardial effusion or other causes of cardiac compression this phenomenon is intensified as follows The increased venous return during inspiration cannot be translated into an increased cardiac output because of the pericardial obstruction to inflow On the other hand, the increased pulmonary vascular capacity during inspiration diminishes the venous return to the left heart The combination of impaired venous inflow and the enhanced pulmonary capacity and retention of blood during inspiration cause the reduction in left ventricular output and in size of the pulse (paradoxical pulse) A pulsus paradoxicus may also be observed in cases of tracheal obstruction and other conditions associated with exaggerated respiratory excursions and therefore with an abnormal increase in pulmonary vascular capacity during inspiration Other explanations have been offered by Wenckebach[11] and by Gauchat and Katz[40]

Inspiratory swelling of the cervical veins commonly accompanies pulsus paradoxicus in cases of pericardial effusion (and constrictive pericarditis) but is absent when the pulsus paradoxicus is due to laryngeal stenosis etc The cervical veins swell because the increased venous return during inspiration cannot be handled by the compressed right atrium with its high intra atrial pressure Normally the increased venous return is adequately received and ejected without permitting a rise in venous pressure or venous distention

General Signs

Fever, sweating weakness and loss of weight have already been mentioned A polymorphonuclear leukocytosis is usually present its severity in proportion to the height of the fever In cases of tuberculous pericarditis however there is usually a relative leukopenia or normal white blood count, even with moderate fever Very marked leukocytosis and polynucleosis suggests a bacterial suppurative pericarditis In rheumatic pericarditis pallor and anemia are often prominent features

The *general appearance* of the patient with pericardial effusion is noteworthy He is anxious suffering restless cyanotic or pale and assumes a characteristic posture Usually he sits up completely and leans far forward Rarely the patient assumes the knee chest position (signe de la prière Mahométane), this is observed also in occasional cases of mediastinal neoplasms or lymphomata

ROENTGENOLOGY

Roentgenologic examination may suggest or confirm the presence of a pericardial effusion[1] Its value is greatly increased if serial films are taken at brief intervals and if the patient is examined in both the recumbent and upright (or sitting) positions Roentgenologic abnormalities, like the abnormalities in physical signs depend essentially on the size and distribution of the effusion and not on the intrapericardial pressure It is doubtful whether effusions of less than 250 cc in adults produce a significant effect on the cardiopericardial silhouette But in infants and children 150 cc or less may suffice to alter the shadow The following are the most valuable roentgenologic signs (Fig 115)

1 The well-demarcated normal outlines of the individual cardiac chambers and great vessels are obliterated, resulting in a smoothing of the cardiac borders with loss of the angular curves In particular, the waist of the silhouette on the left border (pulmonary arterial segment) is filled out to give a straight or slightly convex left cardiac outline A pear shaped or water bottle type of silhouette results

2 The vascular supracardiac shadow becomes shortened and somewhat widened due to the filling of the superior recess in front of the great vessels by fluid Widening is due also to engorgement of the superior vena cava

3 The posterior inferior recess (as viewed in the right anterior oblique or lateral view) is normally demarcated by a straight line or one that is slightly concave posteriorly When an effusion forms the fluid encroaches early on the clear space in this recess and the straight or concave line becomes a bulge which is convex posteriorly[78]

4 There may be a diminution or almost complete absence of visible pulsations of the heart A wavy undulation may replace the alternating contraction and relaxation The diminution or absence of pulsation may be more clearly demonstrated by roentgen kymography or electrokymography

5 *Serial roentgenograms may reveal rapid changes in the si e of the silhouette corresponding*

to a speedy increase or resorption of the effusion (Fig 115) According to Besterman and Thomas[1] a sudden increase in the cardiothoracic ratio and straightening of the left border were the most consistent and earliest signs of pericardial effusion

6 Induction of pneumopericardium following aspiration of the pericardium is helpful in distinguishing pericardial from pleural effusion as well as in revealing the size of the cardiac shadow[34] (Fig 115) Sacculated effusions may occur chiefly in suppurative rheumatic or chronic pericarditis and localize in regions where cardiac motion is least active, e g, near the great vessels or along the lower right border These sacculated collections of fluid may produce a localized bulge usually on the right cardiac contour, and must be differentiated from aneurysm of the aorta or sinus of Valsalva, a pericardial diverticulum, pleural or mediastinal effusions, or benign pericardial tumors Pericardial effusion may be differentiated from cardiac enlargement by the disappearance in the former of the intersections between vascular, cardiac and diaphragmatic contours on the right and the atrioventricular contour on the left, by absence of the changes in size and shape of the silhouette during the Valsalva and Muller maneuver which persist with cardiac enlargement and by disappearance of the bronchial bifurcation[4]

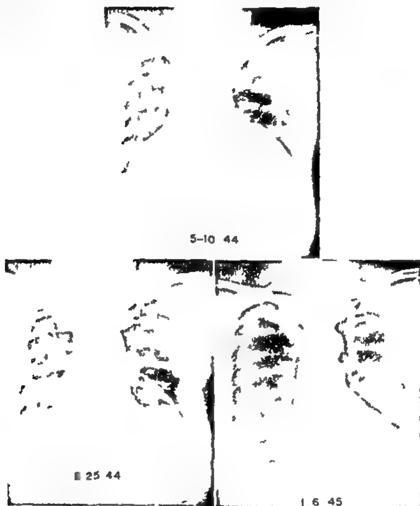


Fig 115 Pericarditis with effusion Upper before paracentesis Lower left after paracentesis with air injected into pericardial space Lower right after recovery seven and a half months later

7 Angiocardiography reveals a characteristic shadow due to fluid surrounding the opacified cardiac chambers[115 61]

THE ELECTROCARDIOGRAM

Distinctive electrocardiographic abnormalities were observed by Winternitz and Langendorf[116] in 46 (61 per cent) of 76 cases and

by Bellet and McMillan[10] in 80 per cent of 57 cases Similarities to the changes in myocardial infarction may indicate that the electrocardiographic abnormalities of acute pericarditis are actually due to associated subepicardial myocardial lesions [106, 111]

The various electrocardiographic changes occurring in cases of acute pericarditis include the following [55, 114, 111, 101]

1 RS T Changes

The most consistent and significant electrocardiographic alteration in acute pericarditis is an elevation of the RS T segment in all three standard leads in leads I and II in leads II and III or in lead I If the RS T segment is elevated in leads I and II or lead I alone it is not depressed in lead III if it is elevated in leads II and III it is not depressed in lead I (Fig 116) Thus the reciprocal elevation and depression of the RS T segment in leads I and III which are characteristic of myocardial infarction are not found in acute pericarditis

The RS T segment differs from that seen in myocardial infarction in that it runs obliquely upward in a straight line or with an upward concavity to a positive T wave In cases of myocardial infarction with RT elevation this segment shows an upward convexity However in later stages of acute pericarditis when the T wave becomes negative the RS T segment may show an upward convexity as with acute myocardial infarction

Since the elevation of the RS T interval may last as briefly as three days and rarely more than three weeks, this abnormality is usually not observed later in the course of the disease Harvey and Whitehill[16] and others failed to note an elevation of the RS T segment in their cases of tuberculous pericarditis which were usually seen more than a month after the onset of symptoms But in two cases of tuberculous pericarditis seen by Holzmann[61] in the first eight days of the disease and in a third seen on the fourteenth day there were elevations of the RT segment in two leads Similar changes were observed by Bellet and McMillan[10] in 2 out of 20 cases

In precordial leads also there may be an elevation of the RT segment or inversion of T waves [10, 107]

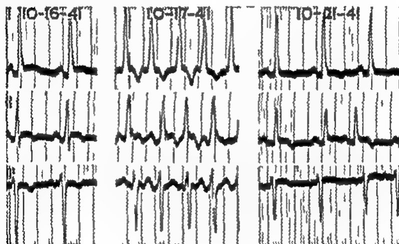


Fig 116 Acute and subacute pericarditis in bacterial endocarditis Progressive changes RT elevations in leads I and II followed by T wave inversions

2 T Wave Changes

The T wave undergoes progressive flattening as the RS T segment returns to the isoelectric line (Fig 116) The upward concavity of the ST segment disappears During this stage Winternitz and Langendorf[114] have also noted a double T wave, a delayed T wave and a linear oblique drop from the R to the T wave

Several weeks after the onset of the pericarditis the T wave becomes inverted Diagnostically an inversion in all three of the standard leads is most significant More often the T waves are inverted in leads I and II or in leads II and III At this stage the ST segment may be curved convexly upward and lead into a sharply inverted T wave resembling the cove-plane coronary T wave of myocardial infarction (p 525)

The inversions of the T wave persist longer than the RS T changes but they usually revert to normal within two to three months In chronic cases of tuberculous pericarditis, inverted T waves may persist throughout the course of the disease

3 Diminution in QRS Voltage

A diminution in the voltage of the QRS complex was noted as a sign of pericardial effusion by Oppenheimer and Mann,[74] who suggested that it was due to short circuiting of the electrical impulses of the heart by the surrounding fluids Low voltages of the QRS and T waves are in themselves insufficient evidence of myocardial or pericardial disease Low voltage of the QRS complex as well as negativity of the T wave is especially frequent in cases of tuberculous pericarditis This electrocardiographic abnormality cannot be well correlated with the size of the pericardial effusion for Harvey and Whitehill[66] noted that following aspiration of a tuberculous effusion the voltage of the QRS complex diminished almost as often as it increased

The duration of the Q T interval is not prolonged as it is in most cases of congestive heart failure, a distinction of limited diagnostic value[104] McGregor and Baskind[64] presented evidence that simultaneous alternation of atrial and ventricular complexes (electrical alternans) is frequently associated with pericardial effusion

Differences in Electrocardiograms of Pericarditis and Myocardial Infarction

The following are the chief distinctions (1) The RS T elevation in pericarditis occurs without the reciprocal RS-T depression in leads I or III seen in myocardial infarction (2) The T wave in pericarditis may be inverted in all three standard leads, this is rare with myocardial infarction unless both aspects of the heart are involved (3) The positive initial deflection in chest leads is rarely absent with pericarditis often absent with acute myocardial infarction (4) Q waves are rarely significant in the standard leads of cases with acute pericarditis, a deep Q_1 or Q_3 commonly accompanies a negative T in the same lead in cases of acute myocardial infarction In combined anterior and posterior infarction there may be an elevation of the RS T segment or an inversion of the T-waves in all standard leads as in acute pericarditis but there is often also a deep Q_1 or Q_3 and the positive initial deflection in the chest lead is usually absent

When pericarditis complicates myocardial infarction, there may be an early elevation of the RS T segments in the standard leads indicative of the pericarditis followed by the characteristic pericardial inversion of the T waves, but often disappearance of the RS T elevation is succeeded by the typical deep Q_1 and negative T_1 or deep Q_3 and negative T_3 of myocardial infarction (see p 525)

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

To diagnose acute pericarditis one must be aware of the possibility of this complication in those conditions which are most often associated with it Precordial pain and fever, unexplained dyspnea and tachycardia, evidence of systemic venous congestion without apparent heart disease, should suggest a search for acute pericarditis A pericardial rub, characteristic water bottle enlargement of the heart, Ewart's sign, a paradoxical pulse, extreme diminution of cardiac pulsations and the characteristic electrocardiographic changes are the most important diagnostic features Aspiration of the pericardial sac may serve both to confirm the diagnosis of pericarditis and to determine the etiologic type Stained smears and cultures of the aspirated fluid should be made and some of the fluid may have to be inoculated in guinea pigs if tuberculosis is suspected Pericardiotomy has been performed to permit direct inspection of the peritoneal sac to remove and examine pericardial fluid by smear and culture and to obtain pericardial biopsies[71b]

Diagnostic difficulty may occasionally arise in distinguishing acute pericarditis from cardiac enlargement of undetermined origin, congestive heart failure, pleuropulmonary disease, pulmonary embolism dissecting aneurysm valvular heart disease when the rub is confused with a murmur myocardial infarction because of precordial pain and somewhat similar electrocardiographic changes, from acute abdominal complications when the pain radiates to the abdomen and from aneurysm or tumor when there is a sacculated effusion Angiocardiography is helpful in distinguishing some of these conditions The circulation time is normal in cases of large pericardial effusion prolonged in cases of cardiac enlargement and heart failure[11] This difference may be used in differential diagnosi

COURSE AND PROGNOSIS

The course and prognosis of acute pericarditis are determined usually by the disease of which it is a complication e g rheumatic fever uremia Suppurative and tuberculous pericarditis usually have a progressive course and fatal outcome but these may be favorably altered by antibiotic and surgical therapy This is discussed further under purulent pericarditis (p 601) and tuberculous pericarditis (p 602)

TREATMENT

As a rule treatment is directed toward the underlying disease and not the pericarditis per se Occasionally the pain of pericarditis is severe enough to require meperidine (Demerol) or morphine for relief during the very acute phase In cases of rheumatic pericarditis full doses of salicylates usually relieve the pain and hasten the resorption of the pericardial fluid (p 851) In benign pericarditis and rheumatic pericarditis adrenocortical hormones appear preferable to salicylates (p 852) The sulfonamides and antibiotics are indicated in the treatment of pyogenic bacterial pericarditis Occasionally recovery is attributed to such drugs alone administered intrapericardially as well as intramuscularly or intravenously But often surgical drainage of the pericardium must be performed (infra) Recovery from acute tuberculous pericarditis may follow streptomycin and isoniazid therapy When the pressing need is to relieve cardiac tamponade pericardial aspiration should be performed and repeated if necessary In cases of recurrent pericardial effusion with cardiac tamponade cure was effected by creating a foramen between the pericardial and left pleural cavities[illegible] The fluid draining into the pleural cavity was readily reabsorbed Pericardial effusion due to malignant neoplasm or lymphoma may be controlled by the instillation of radioactive gold into the pericardial sac[illegible]

PERICARDIAL ASPIRATION

Indications

Aspiration of the pericardium is performed (a) to confirm the diagnosis of pericardial effusion (b) to determine the etiologic agent or (c) to relieve symptoms of cardiac compression

In rheumatic pericarditis pericardial aspiration may be necessary if there is extreme dyspnea and the effect of medication is not rapid enough I have had to remove as much as 1200 cc at one time but usually the removal of 200 to 400 cc provides relief If the diagnosis of suppurative pericarditis is reasonably certain it may be preferable to institute prompt surgical drainage without previous aspiration But the latter may be necessary to relieve acute cardiac tamponade or to prove the diagnosis In cases of tuberculous pericarditis aspirations may be performed for treatment as well as for diagnosis

Site of Pericardial Aspiration

The following are the sites most commonly entered for pericardial aspiration Roentgenograms should be available to aid in determining the most favorable site

1 The fifth left intercostal space about 2 cm inside the left border of percussion dullness is the site most commonly used If there is a distinct apical impulse the needle may be introduced 1 or 2 cm lateral to the impulse

2 The angle between the xiphoid process and the left costal arch is the site recommended when there is a large effusion and the lower portion of the pericardial sac is to be drained It is often used for aspirating suspected purulent effusions because in this region the lung does not cover the heart

3 The right fourth intercostal space 1 cm medial to the right border of cardiac dullness is the site used when most of the pericardial effusion seems to be sacculated on the right side I have had more than a liter of fluid removed through this site in a patient with rheumatic pericarditis after only a few cubic centimeters could be obtained by the first mentioned approach

4 The seventh or eighth left intercostal space posteriorly in the midscapular line the left arm of the patient being elevated to remove the scapula is the site employed when there are evidences of a large effusion with pulmonary compression (Ewart's sign) and fluid cannot be obtained readily elsewhere This site of aspiration has been especially recommended by Conner[33] and by Sutton[illegible] It should not be used in cases of suspected purulent pericarditis because of the danger of infecting the pleura

Technique of Pericardial Aspiration

Pericardial aspiration is performed with precautions as to surgical asepsis The exact

site of insertion of the needle and the subcutaneous tissue are anesthetized with 2 per cent procaine solution A 3 inch aspirating needle of 18 to 16 gauge with short bevel, connected directly or through a connecting piece of tubing to a 20 or 30 cc syringe is inserted through the anesthetized area between the ribs until it is felt to penetrate the resistant pericardial membrane Usually this occurs at a depth of 3 to 5 cm If the posterior site is chosen, a 4 inch needle should be used as the pericardium may be penetrated at a depth of 5 to 8 cm from the skin surface If the effusion is thick a trocar may have to be substituted for the needle in order to avoid blocking the lumen

When the needle is inserted into the left fifth intercostal space it is directed inward and backward toward the spine, when inserted in the left xiphoid costal angle, it is directed backward, upward and slightly inward when inserted in the right fourth intercostal space the needle is directed backward and medially toward the spine, when inserted posteriorly the needle is directed forward and somewhat medially

Gentle suction is made by withdrawing the barrel of the syringe If a free flow of fluid is not obtained, the needle should be tilted carefully in various directions, withdrawn slightly, or carefully inserted somewhat more deeply If no fluid is obtained despite these maneuvers and there is reasonable certainty as to the existence of a pericardial effusion the needle should be inserted in one of the other sites mentioned Sometimes a two-way or three-way stopcock is placed between the aspirating needle and syringe so that no air will enter the pericardium and the fluid may be discharged into a container without disconnecting the syringe If large quantities of fluid are to be removed, the needle may be connected by tubing to a bottle containing a partial vacuum as in performing a thoracentesis for pleural effusion

Occasionally the needle is felt to come in contact with the heart There is little danger from perforation of the ventricular wall, but the needle should be withdrawn slightly if cardiac pulsation is felt Rarely one may cause a hemopericardium by cutting a coronary artery or perforating the thin walled atrium Other dangers of pericardial aspiration include injury of the internal mammary artery and the infection of pleura or peritoneum in cases of purulent pericarditis

SURGICAL DRAINAGE

If the diagnosis of purulent pericarditis is fairly certain, or has been proved by pericardial aspiration, adequate drainage should be obtained by surgical incision Appropriate sulfonamide and antibiotic therapy should be given

Numerous surgical approaches have been suggested including a trans sternal, right or left parasternal, chondroxiphoid, or a combination of trans sternal and left parasternal Often, exposure of the pericardium is effected in the region along the left side of the lower sternum where the pericardium is not covered by lung This is known as the interpleural space or triangle of safety After the superficial tissues are reflected the fifth sixth and if necessary the seventh left costal cartilages are resected and sometimes also a portion of the adjacent sternum[90] Bigger[13] resected the fourth and fifth left costal cartilage and Bunch,[18] the sixth In general the site of exposure should be as low as possible in early cases Ross[85] prefers a chondroxiphoid approach, i e, through the angle between the xiphoid process and left costal margin He splits the rectus muscle to reach the pericardium from below in order to obtain dependent drainage from the oblique pericardial sinus posterior to the heart In late cases of pericarditis especially with large effusions, a posterolateral approach is utilized[103] because of the accumulation of fluid in the posterior recesses behind the heart The seventh rib is resected near the midaxillary line Because of adhesion of the pericardium to the pleura in the cases reported, it was possible to perform a pericardiotomy without producing a pyopneumothorax

Drainage may be maintained with the aid of rubber tubes or tissue, extending down to but not into the pericardial cavity Irrigation with warm normal saline is employed if drainage is unsatisfactory or if the patient fails to do well Two drainage tubes should be inserted if irrigation is employed so that one of the tubes may permit egress of the fluid injected through the other Otherwise the injected fluid may be trapped and may cause cardiac tamponade Some surgeons suture the

opened pericardium to the soft parts and do not use rubber or other drains

After drainage has been established it is important to look for and drain purulent foci elsewhere (especially empyema or osteomyelitis) The persistence of fever even after pericardiotomy should always suggest the possibility of empyema an undrained sacculation of pericardial fluid or a suppurative focus elsewhere

INDIVIDUAL FORMS OF PERICARDITIS

RHEUMATIC PERICARDITIS

This is probably the most common type of pericarditis and is part of a rheumatic pancarditis [101] Its clinical features are discussed in the chapters on rheumatic fever

UREMIC PERICARDITIS

This occurs in the end stages of renal insufficiency as noted by Bright[17] and emphasized by Taylor [104] Pathologic studies reveal a pericarditis in 8 to 45 per cent of cases of nephritis [6, 8, 11] In the presence of uremia regardless of etiology pericarditis probably occurs in more than 50 per cent of cases Wacker and Merrill[108] reported that a pericardial rub was heard in 18 per cent of 77 cases of acute renal failure whereas 22 of 43 patients with chronic renal failure had clinical and pathologic evidence of pericarditis

The pericarditis is usually of the dry fibrinous type but there may be a sterile serofibrinous or hemorrhagic effusion [7, 8] Not infrequently there is a terminal secondary bacterial infection The development of uremic pericarditis has been related to metabolic chemical alterations in the blood Healing and the formation of fibrous adherent pericarditis occur in those patients who survive several weeks after onset of the pericarditis

The pericarditis is asymptomatic and its diagnosis is made by discovering a pericardial rub which is occasionally heard in the left interscapular region [1] as well as in its more common precordial location Death usually occurs within one to three weeks after onset of the pericarditis[3] but survival for months is not as uncommon as is generally believed [8, 66] Remissions and recurrences of uremic pericarditis have been noted [66] Six out of 14 patients with pericarditis due to acute renal failure survived [108]

BACTERIAL (PURULENT) PERICARDITIS

This was one of the commonest forms of pericarditis [89, 93] but is encountered less frequently since antibiotics have become widely used The causative organisms are usually the staphylococci the pneumococci and hemolytic streptococci but a variety of other microorganisms are occasionally responsible including the meningococcus [75] Hemophilus influenzae[117] and P tularensis [96] In one case of tularemic pericarditis constrictive pericarditis developed [93]

A purulent pericarditis arises (a) by direct extension of an intrathoracic infection (b) by hematogenous bacterial dissemination (c) by traumatic introduction of bacteria through the chest wall or (d) occasionally by extension or perforation of the diaphragm from a subdiaphragmatic suppurative focus such as a liver abscess [111] Osteomyelitis staphylococcal or streptococcal sepsis pneumococcal or streptococcal empyema especially of the left pleural cavity, are common preceding diseases Bacterial pericarditis may be fibrinous at its onset and then serofibrinous or serohemorrhagic before it becomes purulent

The clinical features of purulent pericarditis are obscured by those of the general or local primary disease Fever leukocytosis and toxemia are common Unexplained dyspnea with or without cyanosis cervical venous engorgement a falling blood pressure and weak rapid pulse are indicative of purulent pericarditis especially in the presence of the usual causative conditions The presence of a pericardial rub is diagnostic Electrocardiographic changes (RT segment elevations) and fluoroscopic evidence of pericardial effusion or of minimal cardiac pulsation are confirmatory

Early and adequate antibiotic therapy of the primary infection prevents the development of a bacterial pericarditis The mortality of practically 100 per cent for medically treated cases of suppurative pericarditis has been reduced to between 25 to 50 per cent by instituting surgical drainage [103, 91] The combination of chemotherapy antibiotics and early surgical drainage (p 600) has further greatly reduced the mortality Recovery depends on simultaneous adequate surgical and medical therapy of other suppurative foci as well as the pericarditis

TUBERCULOUS PERICARDITIS

This occurs in about 1 per cent of all autopsies[58] and in about 5 to 10 per cent of those on tuberculous subjects[49, 81] There is a striking predilection for males and for the aged But it occurs frequently in young adults or children[78] Among 27 patients with tuberculous pericarditis in the Armed Forces, 25 were males 22 were below the age of 30 and 16 (59 per cent) were Negroes, although only 1 per cent of the Armed Forces were Negroes[44]

Pathogenesis

Tuberculous pericarditis arises by contiguous extension of tuberculous lesions of the hilar or mediastinal lymph nodes, or of pleuropulmonary tuberculosis[illegible] There may be direct contact,[55] or infection of the pericardium may result from retrograde lymphatic extension More rarely tuberculous pericarditis results from hematogenous dissemination, but the pericarditis is usually an insignificant element in the generalized miliary tuberculosis Although pathologically tuberculous pericarditis is always secondary to tuberculous lesions elsewhere, clinically it may appear as the sole or primary manifestation[78, 95]

Pathology

The pericarditis starts as an acute fibrinous reaction which is followed by a subacute or subchronic stage of effusion and pericardial thickening The thickening is due to the development of tubercles, caseous masses and connective tissue Even in the chronic stage characterized by fibrosis there may be large persistent collections of serofibrinous or hemorrhagic fluid or occasionally cheesy pus Eventually the pericardial layers become adherent to each other and to the myocardium or neighboring structures and may cause constriction of the heart (p 608) Calcification of the pericardium may appear

Clinical Picture

The clinical picture is often vague and usually overlooked The onset is insidious, with symptoms such as weakness fatigability, loss of weight anorexia and low grade fever[21] *Cough* may be a prominent and early feature but expectoration and hemoptysis are uncommon Precordial pain may or may not be present and is rarely as severe as with rheumatic pericarditis There may be a friction rub in the early stages of the disease This may last from two days to three weeks[85] Fever may be absent but usually it is high and swinging[46]

When an effusion develops, as it almost always does, the patient suffers from *dyspnea* and other evidences of circulatory embarrassment Owing to cardiac compression the cervical veins become engorged, the venous pressure elevated, the liver enlarged and there may be subcutaneous edema and ascites A pronounced tachycardia is common The clinical picture may simulate that of congestive heart failure or chronic constrictive pericarditis[8] In the acute and subacute stages the clinical picture may be that of a chronic wasting disease with unexplained pyrexia There may be physical signs of a pericardial effusion Pleural effusions are commonly associated[illegible, 48] Atrial fibrillation and partial heart block have been noted

Diagnosis

The diagnosis involves recognition of the pericarditis and determination of the tuberculous etiology It should be considered in cases of unexplained fever and/or congestive heart failure, especially in elderly males who present no evidence of cardiac disease The diagnosis of pericarditis may be supported by the presence of a pericardial rub, paradoxical pulse, and roentgenologic signs of pericardial effusion and inverted T waves in the electrocardiogram Early diagnosis has become extremely important since the availability of effective antibiotics

The etiologic diagnosis can be made only by aspirating the pericardial effusion and discovering the organisms in the centrifuged specimen or by determining their presence through inoculation of a guinea pig If a hemorrhagic effusion or one of very large size (over 1000 cc) is obtained, a tuberculous etiology[117] is suggested After aspiration an artificial pneumopericardium may be produced by the injection of air and a small heart demonstrated roentgenographically This and the absence of murmurs and of leukocytosis help to differentiate tuberculous from rheumatic pericarditis with effusion

Prognosis

Formerly the outcome was generally unfavorable death occurring in 50 to 85 per cent within three to six months[illegible, 44, 117] Death usually occurs from cardiac failure or miliary tuberculosis With the introduction of streptomycin and isoniazid treatment of tuberculosis

there has been a brilliant improvement in the rate of recovery [85 ■ 87] Goyette et al reported an over all mortality of 8 per cent, or 15 per cent in the definitely proven cases treated with these antibiotics

Treatment

Rest in bed and general supportive measures are necessary during the acute stage Analgesics or narcotics may have to be administered if pain is severe Repeated aspirations may have to be performed but only when these are necessary for diagnosis or to relieve dyspnea or severe systemic congestion Generally half as much air is replaced as the amount of fluid removed [113] The fundamental and specific therapy consists of the administration of 300 mg of isoniazid daily and 2 gm of streptomycin every third day [44] This is continued for a minimum of 4 months and preferably for 8 to 12 months Or it may be continued for at least 3 months or preferably for 6 months after cessation of all activity [44] Five of the 27 patients studied by Goyette et al [44] developed constrictive pericarditis If constrictive pericarditis develops pericardiectomy (decortication) is performed only after the tuberculous process becomes inactive with the aid of antibiotic therapy [47] However occasionally in such cases it is necessary to operate even during tuberculous activity if the patient s condition grows steadily worse and the venous pressure rises despite the fact that the pericardial cardiac shadow decreases in size [■ ■]

ACUTE BENIGN PERICARDITIS

This is a nonspecific form of acute serofibrinous pericarditis of unknown cause [7 64] It has been attributed to a viral infection or a hypersensitivity reaction without noteworthy evidence It is being recognized with increasing frequency in recent years [20 42 43 43] The disease has been noted chiefly in young adults but has been observed also at all ages from infancy to beyond the age of 60 There is a great predominance of males The pericarditis is commonly preceded by an upper respiratory infection one or two weeks earlier

The onset may be acute or gradual and is characterized by pain in the chest malaise and fever The pain may be localized substernally and radiate widely especially to the neck back and shoulder It is frequently intensified by respiration but also by bodily motion and occasionally by coughing or swallowing Cough and dyspnea occur commonly A pericardial rub is audible in almost every case and usually persists a week or two or occasionally longer A pericardial effusion is usually present and pleural effusion also develops in about one quarter of the cases The pericardial fluid is straw colored or hemorrhagic A moderate leukocytosis is the rule and the erythrocyte sedimentation rate is accelerated Atypical pneumonia may be associated The initial pain and electrocardiographic abnormalities may simulate acute myocardial infarction [64 7 43] Occasionally the electrocardiographic changes persist [20] The disease subsides spontaneously within a few weeks but occasionally produces an adhesive pericarditis The average duration in one large series of cases was 7½ weeks with a range of 2 weeks to 3 months [■] The course is benign but fatal cases have been reported [86 79]

In a follow up of 41 patients for 2 years or longer Carmichael et al [20] obtained a history of more than one attack of pericarditis in 6 and four recurrences in each of 2 patients Recurrent attacks of pericarditis have been reported by others [63 102 43] In one case roentgenologic follow up revealed calcification of the pericardium The large majority of patients were in excellent health

In the differential diagnosis the disease is most frequently to be distinguished from acute myocardial infarction tuberculous pericarditis and rheumatic pericarditis [■ 47] It may simulate acute abdominal disease [79] Pericardial aspiration may be necessary to confirm or exclude the diagnosis of tuberculous pericarditis before embarking on a prolonged program of antibiotic therapy It may also be necessary to relieve cardiac tamponade in cases with large effusions [79]

Despite some favorable reports antibiotics are ineffective in idiopathic pericarditis Adrenocorticotropic hormones usually give a dramatic symptomatic response[87] and should be tried if tuberculosis and other bacterial causes have been excluded

OTHER FORMS

Pericarditis in Acute Myocardial Infarction (p 503 517)

Pericarditis in Periarteritis Nodosa Pericarditis in association with temporal arteritis has been reported [34]

Pericarditis due to Malignant Neoplasms.[14] This is almost always due to extension of primary or secondary malignancies of the thoracic organs, especially carcinoma of the lungs or breast, to the pericardium. There is usually an effusion which is serofibrinous or hemorrhagic but which may become purulent because of secondary bacterial infection. Further discussion may be found in the chapter on neoplasms of the heart (Chapter 45).

Traumatic Pericarditis (Chapter 44).

Postcommissurotomy Pericarditis (p. 675).

Pericarditis in Libman-Sacks Disease (Lupus Erythematosus) (p. 634). Clinically this is only occasionally revealed by a pericardial rub. At postmortem examination I have observed a macroscopic, a local or diffuse fibrinous or serofibrinous pericarditis or a dense universal adhesive pericarditis in 14 out of 23 cases of this disease. Massive pericardial effusion responsible for clinical symptoms has been noted in 2 cases.[6]

Syphilitic (Gummatous) Pericarditis (p. 895).

Actinomycosis of the Pericardium (p. 913).

Coccidioidal pericarditis has also been observed.[60]

Parasitic Disease of the Pericardium (p. 915).

Roentgen-ray therapy has produced pericardial inflammation or a chronic massive pericardial effusion when employed in a case of hyperthyroidism[44] and in a case of carcinoma of the breast, respectively.[16]

Pericarditis in association with infectious mononucleosis has been reported.[7]

Dissecting Aneurysm of the Aorta. A pericardial rub may be heard due either to dissection or perforation into the pericardium or to secondary occlusion of a coronary artery with consequent myocardial infarction.

PERICARDIAL CYSTS AND DIVERTICULA

Congenital true pericardial cysts[5] may be celomic (mesodermal),[109] lymphangiomatous,[111] bronchial or teratomatous.[62] Acquired pericardial cysts may be neoplastic, parasitic or secondary to hematoma. On the other hand, there may be true pericardial diverticula as distinguished from cysts.[110] Certain pericardial outpouchings or diverticula are chronic, encapsulated pericardial effusions or exudates resulting from pericardial inflammations. True pericardial diverticula and encapsulated effusions are termed pseudocysts.

There are usually no subjective symptoms. Occasionally there are chest pressure or pain or other complaint, which may not be due to the diverticulum as such. Rarely the diverticulum points anteriorly and may present as a non-tender rounded mass on the anterior chest wall near the sternum.[7, 26]

The diagnosis of pericardial diverticulum is made by roentgenologic examination as pointed out by Kienbock and Weiss.[31] The diverticulum appears as a sharply outlined or lobulated semicircular, oval or polygonal area protruding from the cardiac silhouette, usually from its lower right contour, occasionally from its left side. It may or may not pulsate. Pulsations present on one examination may disappear after a period of years. Calcification may develop over many years' observation.[5] The preoperative diagnosis of a pericardial celomic cyst has been made by aspiration and injection of air.[39]

HEMOPERICARDIUM

Hemopericardium denotes the accumulation of blood in the pericardial cavity. It should be distinguished from conditions in which pericardial inflammation produces a hemorrhagic exudate as in tuberculous or malignant pericarditis.

The *etiology* of hemopericardium is varied.[32] Essentially it results from rupture of the wall of a cardiac chamber, a coronary artery, the aorta or rarely the pulmonary artery. These structures are either diseased or torn by trauma. Hemopericardium may also be due to scurvy, leukemia or other hemorrhagic diseases. Neoplasms may cause hemorrhagic pericardial effusions which are almost pure blood.

The commonest cause of acute hemopericardium is *myocardial rupture following acute myocardial infarction*.

Rupture of the aorta in its intrapericardial portion with consequent hemopericardium may be the result of (1) syphilitic aneurysm, (2) degeneration or medionecrosis (so-called spontaneous dissection and rupture of the aorta, see p. 555), (3) adult coarctation of the aorta with rupture just above the aortic valve, and (4) mycotic aneurysms burrowing along the aorta into the pericardial cavity.

Trauma of the heart and pericardium is considered elsewhere (Chapter 44).

The pathologic physiology and clinical picture are essentially those of cardiac tampon-

ade (p 593) The degree and rapidity of bleeding are important Usually bleeding is rapid and cardiac tamponade occurs with as little as 250 cc blood in the pericardium There may be sudden death occurring within one hour after rupture of a ventricle Not infrequently hours or days elapse during which the picture of acute cardiac compression develops (p 594) characterized by high venous pressure a falling arterial pressure and a small quiet heart Shock is frequent Other manifestations are determined by the different causes of hemopericardium

Treatment of the hemopericardium per se consists of relief of acute tamponade by pericardial aspiration or if time permits by surgical removal of the hemorrhagic collection followed by suture of the rupture or closure by graft Transfusions and other measures to combat shock are important (See also cardiac trauma p 1059) Constrictive pericarditis may result from organization of a hemopericardium [89]

HYDROPERICARDIUM

Hydropericardium denotes an excessive quantity of transudate in the pericardial cavity It is probable that the normal amount of pericardial fluid is not more than 30 cc but amounts up to 50 cc are not regarded as excessive Hydropericardium is to be distinguished from pericardial effusions resulting from pericarditis

Hydropericardium is usually part of a generalized anasarca of congestive heart failure or glomerulonephritis It also occurs in myxedema in cases of occidental beriberi in the rare cases of scleredema or Buschke s disease [103] or terminally in wasting diseases such as tuberculosis or carcinomatosis even when there is no direct pericardial involvement It may be part of a nutritional deficiency with hypoproteinemia Hydropericardium may result from local causes which interfere with the venous return from the pericardial circulation such as mediastinal tumors tumors of the lung or heart mediastinal lymphomata or tumors of the thymus or mediastinal lymph nodes

The amount of fluid may vary from 100 to several thousand cubic centimeters As a rule there is no interference with cardiac action and no subjective symptomatology Rarely large effusions occur and may require aspiration to relieve cardiac tamponade

PNEUMOPERICARDIUM

Pneumopericardium or the presence of air in the pericardial cavity is uncommon In 1925 Rigler[85] found 73 reported cases including 1 of his own Often the air is associated with fluid which is usually of a purulent nature—pyopneumopericardium [71]

Pneumopericardium results from (1) traumatic perforation (2) perforation of a neighboring air containing organ into the pericardium[85] or vice versa (3) artificial introduction of air into the pericardium either intentionally or accidentally, and (4) possibly by spontaneous formation of gas when the pericardium is infected by gas producing bacilli

When infection by gas bacilli causes air to be present within the pericardial tissue itself the condition is termed pneumatosis of the pericardium

Usually there are no subjective *symptoms* of the pneumopericardium or they are masked by the more serious consequences of the causative condition Occasionally cardiac compression is produced If there is a large quantity of air there may be tympany on percussion of the precordium and metallic or clinking heart sounds on auscultation If both fluid and air are present characteristic loud gurgling or splashing metallic sounds may be audible (bruit de Moulin) There may also be a pericardial rub

Radiologic examination readily reveals the presence of air which is indicated by a laterally delineated area of increased transparency around the cardiovascular silhouette There is usually striking cardiac activity There may be a horizontal fluid level which moves with cardiac pulsations

Treatment may be unnecessary as small quantities of air are readily absorbed Usually treatment must be directed to the more serious primary or associated conditions When these can be satisfactorily treated it may also be necessary to aspirate the pneumopericardium or to provide surgical drainage of a pyopneumopericardium

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Chapter 23

ADHESIVE PERICARDITIS
CHRONIC CONSTRICTIVE PERICARDITIS

Adhesive pericarditis denotes the presence of adhesions between the two pericardial layers, between the pericardium and heart or between the pericardium and various neighboring thoracic structures. Since chronic inflammatory changes are often absent, the term adherent pericardium is sometimes used instead of adhesive pericarditis. The terms fibrous pericarditis or fibrosis of the pericardium may be used when scar tissue with or without active inflammation is present in the pericardium but there are no concomitant adhesions. Adhesive pericarditis of varying degree was found in 1.6 per cent of 8912 necropsies at the Mayo Clinic,[44] in 2.26 per cent of 1000 necropsies at Massachusetts General Hospital,[67] and in 1.4 per cent of 9618 autopsies in the Mount Sinai Hospital, New York.[61]

Concretio cordis (internal adhesive pericarditis) denotes adhesion, usually extensive, between the parietal layer of the pericardium and the visceral layer (epicardium). There may be partial or complete obliteration of the pericardial cavity.

Accretio cordis denotes the adhesion of the pericardium to neighboring extracardiac structures. It is often associated with internal adhesive pericarditis with or without cardiac compression. *Mediastinopericarditis* is a form of external adhesive pericarditis in which there is extensive scarring of the mediastinal structures with adhesion to a thickened pericardium. There is no definite evidence that the adhesions cause either circulatory disturbance or cardiac hypertrophy.

The lesions known as *milk spots* or *soldiers patches* are milky white, occasionally cloudy, irregular or oval flat plaques of hyalinized fibrous tissue. They are usually situated on the anterior surface of the right ventricle where it is not covered by lung.

CONSTRICTIVE PERICARDITIS

(Pericardial Compression Scar)

DEFINITIONS

Chronic constrictive pericarditis[30, 13] is a dense fibrous thickening of the pericardium, usually of uncertain but frequently of tuberculous or other bacterial origin, which causes chronic compression of the heart and interferes with its diastolic relaxation and filling. This results in systemic venous engorgement and a diminished cardiac output, which produce a characteristic clinical picture. Because the disease is due to an external mechanical impediment without significant concomitant myocardial or valvular lesions, surgical removal of the fibrous pericardial encasing membrane is capable of effecting a rapid and sometimes brilliant result.

The term *Pick's disease* or syndrome is sometimes applied to cases of constrictive pericarditis. Pick[55] described a series of cases characterized by recurrent or progressive ascites attended by little or no edema, in which postmortem examination revealed adhesive pericarditis and an atypical cirrhosis of the liver and fibrosis of its capsule. However, it is doubtful whether Pick's cases represent an homogeneous group.

Polyserositis or *Concato's disease*[16] has sometimes been used interchangeably with constrictive pericarditis. Concato referred to cases in which multiple serous cavities were presumed to be involved by tuberculosis. In my opinion it is questionable whether Concato's disease is an entity. Constrictive pericarditis differs essentially from the usual forms of polyserositis in that it is characterized by

cardiac compression whereas inflammation of the serous membranes is usually absent or occurs only secondarily

ETIOLOGY

Causative Diseases

1 In most cases the cause remains uncertain even after microscopic and bacteriologic examination of the compression scar [11, 2]

2 Tuberculosis is the commonest cause in cases of known etiology [11, 8, 1, 46, 77] The resected scar may be negative for tubercle bacilli in a case previously proven to be tuberculous by culture of aspirated pericardial fluid [37]

3 Bacterial pericarditis especially that due to the pneumococcus occasionally results in constrictive pericarditis Constrictive pericarditis has been reported due to P tularensis [38, 47]

4 Rheumatic fever very rarely if ever causes constrictive pericarditis [49]

5 Occasionally there [illegible] a previous history of acute pericarditis usually of undetermined etiology There are reports of constrictive pericarditis appearing many months or years after an acute pericarditis [1, 30] after chest trauma[4] or after traumatic hemopericardium [1, 54]

6 Neoplastic involvement of the pericardium[73, 27] or a foreign body [73] in the pericardium may produce the syndrome of constrictive pericarditis Constrictive pericarditis was reported in a case of chronic pericardial effusion in which the resected specimen revealed chronic cholesterol pericarditis [16]

Age and Sex

Constrictive pericarditis is essentially a disease of youth although it may occur in persons beyond middle life Most of the proven cases occur between the ages of 10 and 40

There is a predominance of males over females in a ratio of about 3 to 1

PATHOLOGY

The essential pathologic feature of constrictive pericarditis is a dense callous thickening of one or both layers of the pericardium Usually it is 3 to 5 mm in thickness but it may be 1 cm or more It has been described as being as hard as shoe leather The thick pericardium forms an inelastic casement of armor composed of cicatrized fibrous tissue which is incapable of stretching during diastole Microscopically it appears as [illegible] non specific dense avascular hyalinized connective tissue except in those cases which reveal the granulation tissue of tuberculosis or pyogenic infection

Usually both layers of the pericardium are involved the pericardial cavity may be completely or almost completely obliterated Occasionally there are small or large usually sacculated collections of fluid or caseous debris especially in the definitely tuberculous forms of chronic cardiac compression The pericardial scar may extend over the entire cardiac surface and even over the great vessels but it may also be relatively localized From the point of view of circulatory disturbance the scar over the ventricles especially the anterior surface is most important because excellent results are usually obtained by pericardial resection without removal of the scar over the atria and great vessels

Calcification of the scar tissue which may be observed roentgenologically at operation or sometimes only by microscopic examination occurs in at least one fourth to one third of the cases [74, 71, 1] Armstrong found calcification in [illegible] of 10 cases of constrictive pericarditis and only in 2 out of 28 cases of nonconstrictive adherent pericardium In one instance there was true bone The calcification may be so extensive as to form a hard complete shell confining the heart (armored heart or Panzer herz)

The Heart

The heart is usually of normal or less than normal size and the individual fibers may be atrophied In 1728 Lancisi[41] had noted the characteristic syndrome of constrictive pericarditis in a young man with engorged jugular veins enlargement of the abdomen and a small pulse whose heart at necropsy was found to be small and surrounded by a thick completely adherent pericardium Chevers[14] in 1842 distinguished cases of adhesive pericarditis with enlarged hearts and valvular disease from those in which the pericardium was obliterated by [illegible] thick almost cartilaginous deposit the valves were normal and the heart of remarkably small size The latter group presented the clinical picture now associated with constrictive pericarditis Wilks[79] also called attention to such cases but the last 3 of his [illegible] reported cases were probably instances

of rheumatic heart disease and not of constrictive pericarditis

The heart is free from valvular lesions or any of the ordinary forms of cardiac disease In 1 of White's[74] cases there was rheumatic cardiovalvular disease and in another congenital heart disease, both being interpreted as coincidences Similarly the presence of rheumatic heart disease in 5 of 18 cases of constrictive pericarditis reported by Kaltman et al[29] was regarded as coincidental However the superficial subepicardial layers of the myocardium may be involved by the cicatrizing process or by tuberculous or other bacterial infection Myocardial atrophy may be severe enough to cause functional disability

The Liver and Other Viscera

The pathology of the organs other than the heart in cases of constrictive pericarditis, is essentially similar to that in (right sided) congestive heart failure

The *liver* was long considered the site of the basic changes in the disease Curschmann[19] noted in cases of polyserositis an inflammatory coating on the liver (perihepatitis) which he termed the Zuckergussleber (sugar icing or frosted liver) because of the resemblance of the exudate to confectioners' sugar icing The relation of hepatic enlargement and ascites to pericardial obliteration was noted by Rosenbach while Hutinel[36] described the occurrence of hypertrophic cardiac cirrhosis of the liver due to adhesive pericarditis Pick[65] first clearly emphasized that the hepatic changes were caused by venous stasis secondary to the adherent pericardium

As a rule the liver is enlarged in cases of constrictive pericarditis due to venous engorgement In later stages the liver may become small because of atrophy and fibrous contraction The typical nutmeg liver of cardiac failure is usually seen Fibrosis occurs and may be extensive There may be an associated congestive splenomegaly Pick[65] described the hepatic changes as a "pseudocirrhosis to distinguish them from the portal cirrhosis of Laennec

Other pathologic abnormalities may be mentioned briefly The abdominal viscera are congested The kidney and spleen as well as the liver may be somewhat cyanotic and firm due to congestion and fibrosis (cyanotic induration) Pleural adhesions and pleural effusions are usual Pulmonary arteriosclerosis presumed to be secondary to sustained pulmonary hypertension, has been observed Large collections of ascitic fluid occur invariably with occasional secondary peritoneal inflammation and even adhesions

PATHOLOGIC PHYSIOLOGY

That the constricting pericardial scar is the basic cause of the physiologic and clinical disturbances was demonstrated by (a) reproducing the clinical picture in dogs, in which Dakin's solution or other foreign irritating material injected into the pericardial cavity had caused an obliterating constricting pericarditis,[6] and (b) eliminating the clinical manifestations in humans with constrictive pericarditis following resection of the pericardial scar However, to a minor, variable degree, myocardial damage may be a contributory factor in producing physiologic disturbances and the clinical picture

Diminished Diastolic Relaxation and Inflow of Blood

The constricting pericardial scar interferes with normal diastolic relaxation of the heart and thereby impairs the venous inflow into the right atrium and ventricle[14] Constriction of the venae cavae at their entrance into the right atrium is not a factor in producing the circulatory disturbances as indicated by cardiac catheterization and measurement of vena caval and right atrial pressures[31] There is no increase in pressure gradient between the vena cava and the right atrium or between the right atrial mean pressure and the diastolic pressure of the right ventricle The latter excludes significant constriction of the atrioventricular groove The compressing effect of the pericardial scar is best demonstrated by the striking bulging of the heart and resumption of active pulsation when the scar is excised Systolic contraction is usually unimpaired for the heart is capable of expelling what blood it receives although occasionally it suffers as a result of myocardial atrophy

Diminished Cardiac Output

There is a diminished stroke output and minute volume output due to the reduction in venous inflow The reduced cardiac output is due entirely to the diminution in output per beat since the basal cardiac rate is either normal or more often accelerated[11] Diastolic restriction of the heart is such that the stroke output cannot be augmented during exercise, a needed increase in cardiac out

put must be effected entirely by an elevation of the cardiac rate[44]

Increased Systemic and Pulmonary Venous Pressure and Venous Stasis

In both experimental and human constrictive pericarditis there is an early rise in systemic and pulmonary venous pressure But maintenance of an elevated venous pressure despite the diminished cardiac output depends on a greatly augmented circulating blood volume[11] The latter like the increased blood volume of chronic cardiac failure is probably secondary to the deficient cardiac output and the consequent renal retention of sodium and water

Measurements by cardiac catheterization disclose that the pulmonary arterial and pulmonary capillary pressure are elevated[46 ...] indicating that there is also pulmonary congestion due to left ventricular involvement (constriction) as well as systemic congestion Right atrial pressure tracings show an M or W shaped contour with an early diastolic dip followed by a rapid rise to form a plateau[43] The ventricular end diastolic pressure exceeds one third the systolic pressure Similar findings are encountered with diffuse myocardial lesions (p 627) and constricting subendocardial fibroelastosis (p 638)

The augmented circulating blood volume and venous return cannot be accepted normally not because of any right heart deficiency but because of the pericardial impediment to ventricular filling The systemic venous pressure rises because of the disparity between venous return and cardiac filling capacity Intravenous saline infusions given experimentally to human subjects with constrictive pericarditis[44] do not increase the cardiac output in contrast to their effect in acute pericardial effusion[17] This may be due to the fact that in the former it is a non distensible scar which prevents further ventricular filling in diastole in the latter it is an elevated pressure which can be partially overcome

The large circulating volume causes stasis and engorgement in the systemic venous tributaries The circulatory disturbances resemble the inflow stasis due to tricuspid stenosis except that the impediment to right ventricular inflow is due to constriction from without Pulmonary congestion similarly results from a compression scar about the left ventricle with consequent impediment to left ventricular filling and contraction Pulmonary congestion may be partially limited by the diminution of right ventricular output into the pulmonary circulation

CLINICAL FEATURES

The *general clinical picture* resembles that of pronounced right-sided heart failure especially that due to tricuspid stenosis However ascites occurs earlier and is a more prominent feature while edema is less pronounced

Symptoms

The *chief complaints* are most often swelling of the abdomen and dyspnea on exertion

Abdominal swelling is due to the accumulation of ascitic fluid It may be associated with various digestive disturbances, anorexia, abdominal fullness or even pain Sometimes the patient's first complaint is an increase in the size of his waistline or a gain in weight despite limited food intake

Dyspnea usually occurs only on exertion This is presumed to be related to the inability of the heart to increase its stroke output and its limited capacity to augment its minute volume by tachycardia *Orthopnea* likewise occurs when there is pulmonary congestion Occasionally there is dyspnea at rest either because of extensive pleural effusions or because of the reduction in vital capacity due to marked elevation of the diaphragm by ascites but it may be due to pulmonary congestion caused by obstruction to inflow into the non distensible left ventricle

Loss of weight is common in the cases associated with active tuberculous pericarditis but it occurs sooner or later in most cases if allowance is made for serous effusions and edema Weakness fatigability epigastric discomfort and anorexia are occasionally prominent symptoms Syncope occurs occasionally presumably due to inability to increase the cardiac output with exercise

Pulsations of the chest wall are minimal or absent The heart is quiet The apical impulse is difficult to see or feel Broadbent's sign[10] and other signs of systolic retraction of the interspaces are absent

Percussion of cardiac dullness usually reveals a small heart or at least one without significant enlargement But in many cases cardiac enlargement has been noted clinically and roentgenologically This may be due

to the thick scar pleuropericardial adhesions, pericardial effusion or associated rheumatic valvular disease There may be little or no depression of the apex on deep inspiration due to pericardiopleural adhesions Shift of the body from right to left lateral position may be accompanied by little or no displacement of the heart

Auscultation discloses no evidence of organic valvular disease except in cases with concomitant rheumatic cardiovalvular disease Systolic murmurs are occasionally heard as in many normal hearts The heart sounds may appear distant and muffled An early diastolic sound related to rapid ventricular filling is common [52] This extra sound is termed a pericardial protodiastolic sound to distinguish it from the third heart sound or a protodiastolic gallop [44]

The *cardiac rhythm* is usually normal However atrial fibrillation was noted in 4 of White's [74] 15 cases and in 2 of the 9 cases of Stewart and Heuer [71] This arrhythmia may be due to atrial involvement by the compression scar The cardiac rate is usually accelerated

Examination of the lungs usually reveals signs of pleural effusions sooner or later in the course of the disease

Signs of Circulatory Disturbance

1 **Prominent Superficial Veins** The cervical veins are extremely engorged There is no diastolic collapse [5] and no systolic engorgement in contrast with cases of tricuspid valvular insufficiency *Inspiratory swelling of the cervical veins* may be noted but this is often obscured by the constant fullness of the veins

2 **Hepatic Enlargement** Enlargement of the liver due to venous engorgement, is often prominent and occurs early Epigastric pain may be a prominent early complaint due to the enlarging liver The liver may be tender but does not pulsate (a differential diagnostic point with respect to tricuspid insufficiency) However it may be difficult or impossible to palpate the liver if there is massive ascites With longstanding venous stasis atrophy and fibrosis, the liver may occasionally become small

3 **Ascites** *Ascites precox* Ascites is a cardinal feature of the disease The ascites is characterized both by its copious quantity and its tendency to recur However, occasionally it may not recur for months or years, even in the absence of surgical therapy Usually the patient requires abdominal paracenteses every few weeks or months to obtain relief In an oft quoted classic case, 301 paracenteses were performed

A feature of the ascites is its predominance over subcutaneous edema and especially its earlier development (ascites precox) This reverses the usual relationship of ascites and edema in cases of congestive heart failure

The *mechanism* which accounts for the copiousness and early appearance of ascites is obscure The older explanations implicated peritonitis,[40] pleural effusions or cirrhosis of the liver[55] as primary causes Obviously, the pericardial scar and its interference with the inflow of blood is the fundamental cause But the consequent elevation of venous pressure in the inferior caval system should result in peripheral edema at least as early as in ascites The possibility of greater interference with the flow of blood from the hepatic veins than from the inferior vena cava has been suggested on the basis of certain inconclusive observations [25] The adherent pericardium on the diaphragmatic surface of the heart may obstruct lymphatic drainage of the peritoneum which converges onto the diaphragm, and thus may increase the tendency to peritoneal effusion by further elevating the capillary pressure

4 **Subcutaneous Edema** This is often minimal or occurs relatively late Usually, it is less prominent than the ascites It is localized chiefly to the lower extremities or sacral region but occasionally edema of the face rarely of the neck arms and chest wall, is observed when the patient arises in the morning or when he is bedridden

5 **Pleural effusions** are usually present at some stage of the disease They may be of minimal size or sufficiently copious to cause dyspnea and require thoracentesis for relief

6 **Cyanosis** of slight or moderate degree is common This may be due to pulmonary congestion caused by resistance to venous inflow in the left atrium and ventricle or to associated pleuropulmonary disease or peripheral venous stasis

7 **Pulsus paradoxus** is almost always observed if carefully sought Its mechanism has been discussed (p 594)

8 **Abnormal Circulatory Measurements** (a) The *venous pressure* in the antecubital veins is sharply and persistently elevated The aver

age values range between 25 and 35 cm, which are higher than those ordinarily seen with congestive heart failure Sodium restriction and diuresis usually have strikingly little influence on the venous pressure Pressure over the right upper quadrant of the abdomen causes a sharp rise in venous pressure (hepatojugular reflux) even when the venous pressure is not much elevated Exercise and intravenous infusions are more likely to elevate the venous pressure and to a greater height than in normal subjects A fall in venous pressure often follows paracentesis Corresponding to the rise in venous pressure there is also an elevation of the spinal fluid pressure and of the pressure in the thoracic duct [5]

(b) The *arterial blood pressure* is usually low The systolic blood pressure ranges between 90 and 110 mm Hg and rarely exceeds 120 Since the diastolic pressure is usually normal *the pulse pressure is reduced* This is an important sign The pulse pressure averages between 15 and 25 mm Hg Corresponding to the pulsus paradoxus the arterial pressure usually falls on inspiration

(c) The *circulation time* is prolonged [71] As in cases of congestive heart failure the arm-to-tongue time is increased to between 20 and 40 seconds or longer The observations of Stewart and Heuer[71] indicate a prolongation of circulation time through both the right heart and the pulmonary circulation

(d) The *circulating blood volume* as determined in 2 cases by Burwell and Blalock [11] was increased from 30 to 45 per cent above normal

(e) The *cardiac output* is diminished

(f) The *vital capacity* was reduced to between 36 and 68 per cent of normal in the cases studied by Stewart and Heuer [71]

Cardiac catheterization disclosed that the right ventricular diastolic pressure is elevated as in right-sided heart failure and ranges between 6 and 32 mm Hg The right ventricular pressure curve is characterized by a slightly elevated normal or slightly lowered systolic pressure a rapid early diastolic dip followed by a high diastolic plateau indicating a high end diastolic pressure [31, 46, 77] The end diastolic pressure is more than one third that of the right ventricular systolic pressure and the pulse pressure is diminished features which are distinctive from those of right heart failure [77] Catheterization studies also revealed an elevation of pulmonary systolic diastolic and mean arterial pressure and of pulmonary wedge (capillary) pressure [60]

Hypoproteinemia

A reduction of the blood protein concentration is frequent in cases with longstanding symptoms of constrictive pericarditis The reduction is limited to the serum albumin the serum globulin remaining normal or even elevated Reduction in serum albumin favors the development of both edema and ascites (p 201)

The cause of hypoproteinemia in these cases is uncertain It has been attributed to malnutrition (i e to an inadequate intake of protein) to loss of protein in the ascitic fluid which is repeatedly drained and to a reduction in liver function due to chronic passive congestion with consequent inability to fabricate serum protein [43] Stadler and Stinger[68] showed that hypoproteinemia persisted in a child with constrictive pericarditis even though the dietary protein intake was sufficiently high protein nitrogen was retained no albumin was lost and the amount of protein lost by paracentesis was far less than that administered by transfusions Although the usual tests of hepatic function were normal these authors concluded that the inability to regenerate serum albumin was due to liver damage caused by passive congestion Impaired liver function as determined by the Bromsulphalein test was found in all 9 cases of constrictive pericarditis reported by Harrington and Barnes [3]

Roentgenology

Whenever possible large pleural or peritoneal effusions which may interfere with interpretation should be removed before roentgenologic examination of the heart is completed The following are the most significant findings

1 Calcification of the pericardium[66] is the most definite evidence of an adhesive pericarditis but does not necessarily denote constriction The latter is usually present however if calcification is extensive (Fig 117)

2 There is an absence or diminution of cardiac pulsation as observed by fluoroscopy and by roentgenkymography [70] *Electrokymography* usually discloses a characteristic series of alternate flat tops and V depressions[17] (Fig 6 p 10)

3 The cardiac silhouette is usually small or of normal size Although it may appear

slightly or moderately enlarged, in some cases the pronounced enlargement associated with right sided congestive heart failure is not observed

4 The vascular shadow on the right, representing the superior vena cava is usually widened due to engorgement of that vessel

5 Pleural effusion and pleural thickening are common

6 Other roentgenologic observations are less significant There may be any or all of the abnormalities listed above as being associated with external adhesions These include limitation of motion of the heart with change in body position and respiration hazy cardiac border tentlike shadows along the cardiac silhouette and diaphragm abnormal or paradoxical motion of the diaphragm with respiration, and obliteration or encroachment on the retrosternal and retrocardiac spaces

Angiocardiography[16] usually shows dilatation of the superior vena cava, and occasional obliteration of the retrosternal space dilatation of the left atrium and main pulmonary artery

The Electrocardiogram

There is usually a low voltage of the QRS complexes T waves are frequently flattened or inverted in lead I or II or both Corresponding T wave alterations may be seen in chest leads The T wave in limb leads may resemble the inverted coronary T wave of myocardial infarction There may be slurring of the QRS complexes in all leads but no notching[20]

Broad, notched P waves were found in 42 6 per cent of one large series[13] The second notch of the P wave is characteristically taller than the first[26] Fixation of the electrical axis may or may not be present[71] Fixation of the electrical axis in cases of valvular disease with large hearts and external adhesions may be distinguished from that due to constrictive pericarditis by the high voltage of the QRS complex in the former group of cases Atrial fibrillation has been reported in a fair percentage of cases of constrictive pericarditis

The ballistocardiogram frequently shows large abnormal early and middiastolic waves and distortion of the initial portion of the systolic complex[6]

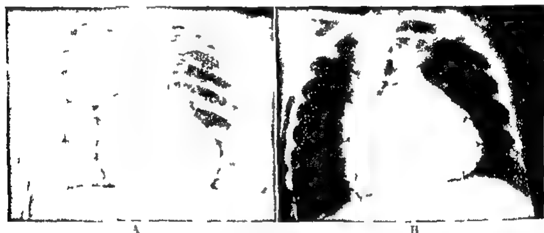


Fig 117 Constrictive pericarditis with dense calcification of pericardium *A* Posteroanterior view *B* Right anterior oblique view

DIAGNOSIS

The diagnosis is usually simple if the condition is borne in mind It is suggested by the presence of signs of congestive heart failure without signs of heart disease Usually the diagnosis is based on the observation of venous engorgement, persistently high venous pressure hepatic enlargement and ascites in a patient without organic valvular murmurs or other evidences of heart disease, and without cardiac enlargement Beck[4] emphasizes the triad of chronic cardiac compression (1) an elevated venous pressure (2) ascites and (3) a small quiet heart Confirmatory signs are a small and usually paradoxical pulse low systolic blood pressure and especially a *low pulse pressure,* roentgenologic finding of diminished cardiac pulsations and occasionally of pericardial calcification, and finally little or

no change in objective signs despite active treatment of congestive heart failure. A history of a pericardial rub or effusion, especially of tuberculous or other bacterial origin, may be helpful. Not infrequently the patient is observed in the febrile phase of acute pericarditis (usually tuberculous) and signs of impaired cardiac filling appear as the acute disease subsides.

In a number of reported cases cardiac enlargement was said to be present.[74, 75] Occasionally elevation of the diaphragm by ascites, the presence of pleural effusions, the haziness of the cardiac borders and the width of the thick pericardium lead to an erroneous roentgenologic interpretation of cardiac enlargement. The differential diagnosis may be difficult when there is coexistent rheumatic cardiovalvular disease.[29]

DIFFERENTIAL DIAGNOSIS

The prominence and early development of ascites may suggest the presence of cirrhosis of the liver or of a chronic (usually) tuberculous peritonitis with or without polyserositis.

Cirrhosis of the liver may be excluded by the finding of venous congestion in the superior caval as well as in the portal system, i.e., by the observation of cervical venous congestion and elevation of the venous pressure in the upper extremities.

I have seen one case which was at first erroneously diagnosed as constrictive pericarditis because of evidences of obstruction of both the superior and inferior vena caval systems without physical signs of cardiac disease. But the correct diagnosis of *multiple venous thrombosis* (of unknown etiology) was made ante mortem chiefly because of the presence of a visible collateral venous circulation on the chest wall, which does not occur in cases of constrictive pericarditis.

Congestive heart failure due to primary cardiovalvular or pulmonary disease is distinguished by the history and by physical, roentgenologic and electrocardiographic evidence of the underlying cardiac or pulmonary disease. *Tricuspid stenosis* is distinguished by the concomitant presence of mitral stenosis and often an atrial venous pulse, while in tricuspid insufficiency there is usually a systolic hepatic pulsation and a positive cervical venous pulse.

TREATMENT

Once the diagnosis of chronic constrictive pericarditis is made, the only satisfactory treatment is surgical—partial pericardiectomy (decortication of the heart). However, signs of cardiac compression due to tuberculous pericarditis may disappear without operation if the tuberculous pericarditis is cured by streptomycin-isoniazid therapy[7] (p. 603).

Preoperative Management

Bed rest for a few weeks, minimal sodium intake, salt-free albumin if there is pronounced hypoproteinemia, mercurial diuretics, removal of large abdominal, pleural or pericardial effusions are important preoperative measures (Chapter 11). Digitalis is not indicated in the classic case with normal or small heart and without myocardial or valvular disease. However, digitalization should be effected rapidly if the atrophic heart is unable to handle the increased inflow after cardiac decortication. Venesection is said to be contraindicated, for the high venous pressure serves the useful purpose of maintaining a desirable pressure head to secure an adequate inflow of blood into the heart despite pericardial compression of the heart.

In the active tuberculous stage, medical therapy with streptomycin, isoniazid and/or para-aminosalicylic acid (*PAS*) is employed. Signs of cardiac tamponade during this phase may be due to pericardial effusion and may be relieved by aspirations. Constriction by scar tissue may be thus avoided. If this develops despite the above treatment, operation is indicated.

Operation

If there is active pericardial infection the operation should be deferred if possible until the tuberculosis or other infection is controlled by antibiotics. However, Blalock and Levy[9] and also Beck[4] have had successful results in some cases in which pericardiectomy had to be performed because this seemed to be the only hope of reversing a downhill course. Blalock and Levy decided on operation for patients with active tuberculous pericarditis and cardiac compression if the patient became sicker and the venous pressure rose even though the pericardiocardiac shadow, by roentgenologic examination, was becoming smaller.

The *operative technique* has been described by various surgeons (see Schmieden[63] Churchill[15], Blalock and Burwell[8] Beck[5] Heuer and Stewart[34], Harrington and Barnes[2, 35]) The operation of decorticating the heart from its confining scar was first suggested by Delorme[21] first carried out successfully by Rehn[56] and in this country by Churchill[15] It is important to provide an adequate exposure of both the left and right ventricles This may be obtained by excision of the left sixth rib from spine to sternum with division of the fourth and fifth costal cartilages close to the sternum Sometimes the sternum is transected transversely As a rule the scar is first dissected from the left ventricle and when this is free to receive a greater amount of blood than previously the right ventricle is decorticated Care must be taken to avoid injury to the coronary arteries and the phrenic nerve The pericardial scar is removed from as much of the anterior surface of the ventricles as possible without too great danger to the patient s general condition and with caution to avoid tearing the myocardium or injuring the anterior descending coronary artery Only occasionally is it possible to resect the pericardium from the posterolateral posterior and diaphragmatic surfaces but this is usually unnecessary However Harrington and Barnes[2] emphasize the need for wide pericardial resection including the apex of the heart and diaphragmatic surface of the right ventricle There is similar difference of opinion as to the need for removal of scar tissue from the thin walled right atrium which tears easily and from the venae cavae Harrington and Barnes believe that when the constricting pericardium is calcified as much of the calcium as possible should be removed from the right atrium the atrioventricular sulcus and the area around the orifices of the venae cavae In most if not all cases removal of the scar from both ventricles is the essential procedure in the operation whereas dissection of the membrane from the venae cavae and atria is unnecessary and involves considerable risk of bleeding The criterion of adequate pericardial resection is the successful release of the heart and visible increase in cardiac pulsation

Postoperative Management

The patient is usually placed in an oxygen tent in semi Fowler s position and kept there for several hours or a few days But some surgeons employ oxygen only if specially indicated Fluids are limited Beck[5] avoids the administration of fluids intravenously because the atrophic heart may not be able to cope with both the additional inflow of blood and the fluids In fact venesection is sometimes indicated if there is a sharp rise in venous pressure Digitalis or quinidine may be required postoperatively to control atrial fibrillation or other cardiac irregularities But these are usually transient and subside spontaneously

Convalescence is usually rapid and the patient is ambulatory in four to six weeks The restriction of sodium and the administration of diuretics should be continued until there is no longer any evidence of edema or serous effusions

PROGNOSIS WITH AND WITHOUT OPERATION

The outlook of patients with constrictive pericarditis is almost uniformly poor if pericardiectomy is not performed The patient is a semi or complete invalid Sooner or later he becomes bedridden, weak and emaciated He suffers extremely from the recurrence of copious ascites and the need for frequent paracentesis But to evaluate operative results it must be noted that occasional unoperated patients survive for many years or decades that sometimes without apparent cause abdominal effusions remain stationary or do not recur for years after aspiration, and finally that in occasional patients fair results may be obtained by active, prolonged, dehydration therapy

In comparison with medical treatment the results of pericardiectomy are brilliant when the operation is properly performed on appropriate cases Between 50 and 75 per cent are cured or greatly improved[5, 15, 34, 8, 53, 13, 46, 2] The mortality has ranged between 15 and 25 per cent but has diminished with increased surgical experience The favorable effects of the operation may be noted early During the operation the heart should enlarge and herniate into the pericardial defect created by resection thus indicating the removal of compression The pulsations become noticeably greater the pulse stronger and the systolic pressure and pulse pressure should increase Cyanosis often disappears The patient usually feels subjectively better when he

becomes conscious and breathing is easier The extremities feel warmer and cervical venous engorgement may be less prominent although still present Sometimes a considerable diuresis occurs within 48 hours after operation, more often it is delayed

Whereas occasional cases show a rapid and progressive improvement immediately after operation most successful cases require three to six months for a cure In particular enlargement of the liver moderate engorgement of the cervical veins and some elevation of venous pressure may persist after other evidences of the disease have disappeared Pulmonary hypertension may not be alleviated when the left ventricle is insufficiently released from its scar[61] Imperfect clinical improvement and incomplete restoration of normal hemodynamics may be due in part to myocardial atrophy and fibrosis but chiefly to inadequate decortication of the ventricular scar When a successful result is obtained not only do the serous effusions and edema disappear but the abnormal circulatory measurements are completely or almost completely restored to normal [9, 71]

CALCIFICATION OF THE PERICARDIUM

Incidence and Etiology

Calcification occurs as a secondary degenerative change complicating chronic inflammation of the pericardium It is observed in cases of rheumatic pericarditis[35] pneumococcus[4] or other bacterial (purulent) pericarditis chronic tuberculous pericarditis traumatic pericarditis [4, 78] and in many cases of constrictive pericarditis of unknown etiology (p 609) Calcification of the pericardium may occur without determinable cause in apparently healthy persons[45] It has been found in individuals with a negative tuberculin but a positive histoplasmin skin test[7]

Pathology

The calcium may form discontinuous plates or bands or it may form almost a complete shell 1 to 2 cm thick (armored heart or Panzerherz) Predominant localization is believed to occur where cardiac pulsation is least The commonest sites of calcification are the coronary sulcus the diaphragmatic surface of the right ventricle the right atrium and the sternal aspect of the right ventricle in the order named

Calcification occurs in the parietal or epicardial layers usually in both As a rule there is an associated adhesive pericarditis with complete or incomplete obliteration of the pericardial cavity or rarely a purulent pericarditis[43] Occasionally ossification is also associated with the deposition of lime[1]

Clinical Features

Calcification of the pericardium, per se usually causes no disturbance in cardiac physiology and no clinical subjective symptoms However in many cases there is a clinical picture of constrictive pericarditis or of congestive heart failure due to associated cardiovalvular disease Calcification of the pericardium may be associated with electrocardiographic abnormalities such as RS T depressions and T wave inversions[45]

Roentgenology and Diagnosis

Calcification of the pericardium is recognized by roentgen ray examination[4] or is first discovered at operation or at necropsy A tabular review of over 70 cases was presented by Rummert[19] Stehr[43] reported 12 of his own cases in 1939 Roentgenologic discovery is most likely if both teleoroentgenographic and fluoroscopic examinations are made,[46] and especially by tomography Calcification is most apt to be seen in the lateral and oblique views especially where the cardiopericardial and sternal shadows fuse The calcium may appear as dense sickle shaped shadows or as massive irregular plates streaks or branched forms Multiple roentgenologic views are often necessary to prove the pericardial site of calcification Pericardial calcification must be distinguished from calcification of the valves which is centrally located in all views and shows extensive motion from calcified thrombi which are oval masses usually near the cardiac apex, and from calcification of the coronary arteries of adjacent lymph nodes or of the costal cartilages

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Chapter 24

MYOCARDITIS AND MYOCARDIAL DISEASE OF OBSCURE ORIGIN

Almost every cardiac disease is associated with myocardial involvement The most frequent and most significant types of myocardial disturbance will be presented in the individual chapters devoted to the etiologic forms of cardiac disease This chapter is concerned with those instances of myocarditis and myocardial disease which cannot be classified under the major etiologic forms of heart disease

MYOCARDITIS

The term myocarditis was first employed by Sobernheim[35] to denote inflammation of the myocardium Currently it refers to the myocardial lesions and symptoms associated with infectious diseases infections and intoxications as well as to myocardial inflammatory changes of obscure origin [36, 4, 8] It has been applied also to certain essentially degenerative lesions of the muscle fibers encountered in cases of diphtheria and other infectious diseases On the other hand myocarditis is no longer considered a proper diagnosis in cases of myocardial infarction due to coronary artery occlusion, even though an inflammatory reaction is elicited by injury of the muscle fibers Diffuse and focal fibrosis of the myocardium associated with hypertensive and coronary artery disease should not be classified as chronic myocarditis or fibroid myocarditis since the fibrous scars are due to myocardial ischemia and not to the healing of inflammatory lesions

Myocarditis itself is rarely an adequate diagnosis since it may be due to a variety of causes Whenever possible the etiologic factor should be included such as the causative organism (e g meningococcus myocarditis) or chemical agent (phosphorus poisoning) or the primary disease which either produced the myocarditis (e g rheumatic fever) or of which the myocardial inflammation is a part (e g subacute bacterial endocarditis) Myocarditis is often only a pathologic anatomic diagnosis since the lesions may be insufficient to cause clinical symptoms or the latter may be overshadowed by other clinical features of the primary disease The finding of microscopic lesions of myocarditis in necropsy cases has led to the erroneous conclusion that the clinical diagnosis of myocarditis should be made much more often [36, 43] The clinical significance of the microscopic myocarditis should not be exaggerated This applies also to non specific electrocardiographic changes encountered in many acute infections

Classification

Myocarditis is sometimes classified as acute and chronic The division is often indistinct Myocarditis may be further subdivided into (1) infectious and toxic myocarditis (2) suppurative myocarditis and (3) idiopathic or isolated (Fiedler's) myocarditis Saphir[36] classified myocarditis as (1) myocarditis following infections with or without endocarditis, (2) specific myocarditis e g rheumatic tuberculous, etc , (3) myocarditis due to chemical poisons physical agents or hypersensitive states and (4) isolated myocarditis (without associated disease)

Etiology and Incidence

The *incidence* of myocarditis is discussed with the individual causative diseases in later chapters The available data are unreliable first because the pathologic diagnosis can be made in only a small percentage of cases owing to the relatively low mortality in infectious diseases and second, because these cases, being the most serious, are not representative of the disease On the other hand the incidence based on clinical cases is unreliable because of unsatisfactory and varied criteria employed by different observers for the diag

nosis of clinical myocarditis When routine serial electrocardiograms are made in infections, the incidence of myocarditis has been reported as being much higher than is generally supposed But it is uncertain whether the electrocardiographic changes observed are actually due to inflammatory lesions in the myocardium There is often a lack of correlation between pathologic changes electrocardiographic abnormalities and cardiac symptoms or signs

According to Saphir[96] 240 cases of myocarditis (4 3 per cent) were encountered in 5626 consecutive autopsies on adults 186 of the cases were nonrheumatic In a similar study among children the incidence of myocarditis was 6 8 per cent [97] Gore and Saphir[42] reported 1402 cases of myocarditis among soldiers studied at autopsy 90 per cent of which were rheumatic In the majority of cases the diagnosis was not suspected clinically These observers listed some fifty conditions associated with myocarditis, including bacterial rickettsial viral fungal protozoal and helminthic infections, glomerulonephritis sulfonamide sensitivity carbon monoxide poisoning heat stroke and burns Although they stressed the point that the clinical diagnosis could have been made frequently on the basis of symptoms and signs and electrocardiographic changes many of the signs listed are those of shock probably due to peripheral vascular failure and not to myocarditis while manifestations of myocardial failure are uncommon

Rheumatic fever is the predominant cause of clinically significant myocarditis (Chapter 31) *Diphtheria* may induce a severe myocarditis (p 902) but both the diphtheria and especially the complicating myocarditis are relatively infrequent *Subacute bacterial endocarditis* (Chapter 34) is accompanied by a high incidence or an invariable occurrence of microscopic cardiac lesions The occurrence of unexpected death following an acute tonsillitis or nasopharyngitis presumed to be due to a myocarditis demonstrated at autopsy,[17, 43] is very impressive but still remains a comparative rarity in proportion to the total number of cases of upper respiratory infections or of myocardial disease A large number of other infections and toxic agents which are responsible for occasional instances of clinical myocarditis and for more frequent instances of histologic myocarditis are discussed in Chapter 36

Pathology

Acute myocarditis is often subdivided pathologically into parenchymatous and interstitial forms In the former the predominant or primary changes involve the myocardial fibers themselves, in the latter the inflammatory lesions are situated chiefly or primarily in the interstitial tissue As a rule, however the lesions involve both the parenchyma and interstitial tissue and it is impossible to decide which structures were first affected

Parenchymatous myocarditis is best exemplified by certain cases of diphtheria, but similar though less severe changes are observed in cases of typhoid fever, scarlet fever, pneumonia and other infectious diseases The fundamental lesions are degenerative alterations of the muscle fibers These include cloudy swelling hyaline or vacuolar (hydropic) degeneration, granular degeneration waxy degeneration and fatty degeneration (p 126) Brown et al [16] reported a case of focal necrotizing myocarditis without interstitial infiltration, in which the clinical picture, thought to be that of acute myocardial infarction, was terminated by sudden death The muscle fibers may be only slightly affected or focal or large areas of muscle tissue may be destroyed and replaced by productive inflammation or fibrosis Associated interstitial inflammatory changes appear early or late as a reaction to the muscle injury or as part of a universal myocarditis

Interstitial myocarditis is typified by the myocardial changes in rheumatic fever (p 816) An essentially or primarily interstitial myocarditis is observed also with meningococcic infections, trichinosis so-called isolated (Fiedler s) myocarditis and occasionally in cases of scarlet fever, influenza and typhoid fever The lesions are usually diffuse and consist of varying degrees of edema and infiltrations of neutrophilic or eosinophilic leukocytes lymphocytes, mononuclear cells, occasional plasma cells and of histiocytes and fibroblasts Eosinophilic and giant cell granulomatous myocarditis has been noted, in one case at least, apparently due to penicillin sensitivity [102] Granulomatous arteritis has been observed in the myocardium of a patient with Wegener s granulomatosis [31] In rheumatic myocarditis a characteristic spe-

cific granulomatous lesion the Aschoff body is frequently observed In mild forms of interstitial myocarditis only focal lesions may occur The muscle fibers may be normal or only little affected but as a rule they undergo some degree of degenerative change atrophy or necrosis

Focal myocardial lesions involving the parenchyma the interstitial tissue or both occur in various bacteremias especially those due to pyogenic organisms or to direct extension from suppurative lesions of the pericardium or endocardium In the latter cases and in bacteremias due to staphylococci hemolytic streptococci and less commonly gonococci and pneumococci a *suppurative myocarditis* occurs The bacteria may produce an arteritis with swelling and necrosis of the adjacent musculature and a reactive infiltration of polymorphonuclear leukocytes Similar foci of necrosis and leukocytes may be the result of bacterial toxins Small or large macroscopic abscesses may result by contiguity from suppuration of the pericardium or endocardium by septic embolization of the coronary vessels with local infarction and softening of the myocardial tissue or by direct bacterial infection through the blood stream Rarely large abscesses develop and may rupture a papillary muscle perforate the interventricular septum or heart or break into the pericardium and cause a suppurative pericarditis

The *gross appearance* of the heart usually presents no characteristic change even though surprisingly diffuse and sometimes severe lesions may be discovered microscopically Sometimes the musculature is soft and flabby and may have a dull parboiled or glassy appearance With suppurative myocarditis miliary abscesses may be seen as yellow dots or streaks surrounded by a reddish zone which yield a drop of pus when cut Cardiac dilatation and hypertrophy may be associated with acute myocarditis especially in cases with congestive heart failure Endocardial (mural) thrombi are found in occasional cases of acute myocarditis

Clinical Picture

There are often no clinical features associated with acute myocarditis as seen pathologically Sometimes the clinical features when present are indistinguishable from and overshadowed by those of the primary disease or of an associated endocarditis or pericarditis or by the manifestations of peripheral circulatory failure The evidences of acute myocarditis may be (1) general symptoms (2) cardiac signs (3) electrocardiographic changes (4) congestive heart failure and (5) embolism

1 **General Symptoms.** These are non specific and include fever leukocytosis weakness palpitation precordial pain and tachycardia They may be due to the primary disease as well as to the myocarditis Tachycardia out of proportion to the fever is suggestive of myocarditis especially in cases of rheumatic fever On the other hand the tachycardia may be evidence of peripheral circulatory failure due to toxemia and especially during convalescence it may be evidence of a labile vasomotor system or of an irritable heart Bradycardia may be present with myocarditis especially in some cases of diphtheria with heart block

2 **Cardiac Signs** A softening or diminution of the first sound has been noted as an early sign of myocarditis[34] The first sound may become indistinguishable from the second sound resulting in a tic tac rhythm (embryocardia) An apical systolic murmur occurs frequently Tachycardia is common These are all inconclusive evidences of myocarditis being frequently present in febrile and toxic states without myocardial lesions A gallop rhythm is indicative of cardiac failure and in the absence of preexisting heart disease suggests a myocarditis if it appears in the course of an acute infection Under the same circumstances cardiac enlargement may indicate the presence of acute myocarditis

3 **Electrocardiographic Changes.** As a result of more frequent electrocardiographic examinations of patients with infectious diseases the incidence of myocarditis is believed to be much higher than was formerly thought Fine et al[35] found abnormalities in serial electrocardiograms which they interpreted as denoting myocarditis in one third of 84 patients suffering from a variety of infectious diseases However it is doubtful whether the electrocardiographic changes are caused by the anatomic alterations observed at autopsy It is more probable that the former are due to electrolyte disturbances especially in potassium to changes in acid base balance or to metabolic or enzymatic disturbances in the

myocardium produced by the primary infection or toxic agent

A variety of *electrocardiographic changes* has been described These will be discussed more fully under the individual diseases Most often there are elevation or depression of the RS T interval, flattening or inversion of the T wave prolongation of the P R interval, or more severe grades of heart block Sinus bradycardia occurs occasionally while extrasystoles are common Atrial fibrillation and flutter may occur, but usually in patients with preexisting cardiac disease The electrocardiographic changes are usually transient and of brief duration but not infrequently persist for several weeks after convalescence

4 **Cardiac Failure** The occurrence of acute myocarditis may be accompanied by the symptoms and signs of cardiac failure Congestive heart failure occurs only occasionally as a result of myocarditis alone except in rheumatic fever On the other hand, congestive heart failure is not infrequently precipitated by an acute infection in patients with preexisting heart disease, usually without a superimposed acute myocarditis Thus the development of congestive heart failure during an infection suggests an acute myocarditis only if there is no associated organic heart disease

More often, acute infections, especially when associated with severe toxemia cause peripheral circulatory failure (shock) This may occur without any significant damage to the myocardium Clinically the patient appears pale and faintly cyanotic and the skin has a grayish hue The extremities and nose are cold and often clammy with perspiration The pulse is rapid, weak and thready The blood pressure and usually the venous pressure also are low The superficial veins are often collapsed Respirations may be rapid but dyspnea is usually absent The exact pathogenesis of this type of failure is still uncertain but except in cases of diphtheritic myocarditis it is not usually the result of acute myocarditis Occasionally both congestive heart failure and shock are associated in the same patient Sudden death has been repeatedly noted in cases of myocarditis complicating acute infections, often following a brief period of heart failure or shock

5 **Pulmonary or other embolism** may complicate cases of myocarditis in which mural thrombosis occurs

Prognosis

This is discussed in connection with the *individual causative diseases*

Treatment

Prolongation of bed rest is indicated when myocarditis complicates an infection Other therapeutic measures are determined by symptoms and particularly by the development of congestive heart failure

ACUTE ISOLATED MYOCARDITIS

An acute *interstitial myocarditis*, of unknown etiology, characterized by a distinctive clinical and pathologic picture was described by Fiedler[33] It is often termed Fiedler's myocarditis Because the inflammatory lesions are limited to the myocardium, while the endocardium and pericardium are unaffected it has also been termed acute *isolated* interstitial myocarditis Primary myocarditis denotes that it is not apparently secondary to any other known causative agent or disease Idiopathic is another descriptive adjective applied to this disease because of the unknown etiology The first two cases in the American literature were described by Scott and Saphir[90] and subsequent studies were reported by Marcuse[69] and others It is doubtful whether the cases included in this category form an etiologic pathologic or clinical entity

Etiology

The cause of this form of acute myocarditis is unknown According to strict criteria, no case belongs under this classification if it follows closely upon an infectious disease or if there is evidence of hypertension, coronary disease previous rheumatic fever or any other known cause of heart disease *But a* history of antecedent respiratory infection or a concurrent respiratory infection is common Most cases occur in the third decade, but some have been reported at diverse age levels from childhood to old age A predominance of males has been noted [redacted]

A variety of causative agents or mechanisms have been postulated to account for these cases of idiopathic myocarditis, including a virus[89] and unknown bacterial toxins Recent pathologic and experimental observations have suggested that the myocarditis may represent an allergic reaction, particularly hypersensitivity to the sulfonamide drugs or penicillin[102] Myocarditis has been reported due to the administration of

serum[71, 75] and to arsphenamine sensitivity.[15] French and Weller[22] reported histologically proven interstitial myocarditis in 55 per cent of 227 patients given sulfonamides in their final illness. The lesions were characterized by eosinophilic cellular infiltrations and by the occurrence of large mononuclear cells of the clasmatocyte type. Similar lesions were produced in the experimental animal by the administration of sulfonamides. However, Fawcett[32] observed no difference in the incidence of interstitial myocarditis before or after the advent of sulfonamide drugs. Nor did he find any evidence that the administration of these compounds shortly before a patient's death was associated with either an increase in the total number of myocardial interstitial cells or an excess of a particular type of cell.

Pathology

The heart is usually dilated and hypertrophied, often strikingly so. Heart weights between 500 and 700 gm. are not uncommon, but the heart may be of normal size.[44] The heart muscle often appears pale and is studded with irregular, yellowish or gray streaks or dots. It may be soft and friable. The pericardium and endocardium are not involved, but intramural thrombi are frequently encountered. The coronary arteries are normal.

Microscopically there is a widespread infiltration of cells in the interstitial tissue. The nature of the cells differs somewhat in the various cases, but they are usually neutrophilic or eosinophilic leukocytes or lymphocytes. Endothelial cells, plasma cells and fibroblasts are also observed, and may predominate. Sometimes the inflammatory changes are characterized by granulomatous infiltrates with giant cells (giant cell myocarditis). There may be evidence of granulation tissue and early reparative changes. The muscle fibers may disclose edema and degenerative alterations, but these are relatively slight. Although the interstitial changes are far more prominent, they may represent a reaction to metabolic, allergic or toxic disturbances in the muscle fibers.

Clinical Features

Often there are no significant symptoms and the diagnosis is made on histologic examination.[49] When cardiac symptoms are manifested, the characteristic clinical picture is one of rapidly progressive congestive heart failure. The onset may be gradual or acute. As a rule, in the beginning fever is absent or only slight. The remainder of the course is one of low fever alternating with afebrile periods. Moderate or high fever may occur toward the end of the disease, less commonly at the outset. Rarely there is a septic febrile course resembling that of bacterial endocarditis. Blood cultures are negative. In a few cases the onset and course resemble those of myocardial infarction,[3, 44] but there is much doubt in at least some of these cases whether they properly belong to the group under discussion.

The outstanding symptoms are dyspnea and weakness. Mild precordial oppression and palpitation are not uncommon. The patient is often apprehensive. There may be a grayish cyanosis of the skin. Eventually there are classic signs of congestive heart failure, including gallop rhythm, enlargement of the liver, peripheral subcutaneous edema, congestion of the superficial veins and occasionally effusions in the serous cavities. Sudden death may occur. The clinical picture may begin with or be complicated by embolization of the pulmonary or cerebral vessels. Hemiplegia and cough with bloody expectoration have been observed.[10] Emboli probably arise in the intramural cardiac thrombi mentioned above. Infarcts of the kidney and lungs have been found at postmortem examination.

The heart is usually enlarged, often considerably so. The heart sounds may be muffled and there may be an apical systolic murmur. Freundlich[33] found the circulation time considerably prolonged and the venous pressure extremely elevated. Extrasystoles are not uncommon and atrial fibrillation has been reported.

The electrocardiogram may reveal no significant abnormalities. Occasionally, as first noted by de la Chapelle and Graef,[19] conduction defects may be disclosed by a prolonged P-R interval and intraventricular block.

The leukocyte count is often normal, especially in the cases with little or no fever, but leukocytosis is not uncommon at some stage of the disease.

Course and Prognosis

The course is unfavorable: cardiac failure is progressively more severe and almost always there is a fatal outcome within a period of weeks or months. In the cases of isolated myocarditis studied by Jaffé[34] in Venezuela, the heart failure followed a

chronic course lasting months or years Idiopathic isolated myocarditis with progressive fatal course but of subacute or chronic duration has also been reported by Boikan[13] and by Franz[37] About 15 per cent of the patients die suddenly[43] the clinical picture being that of acute cardiac failure with pulmonary edema When an occasional patient is said to have survived there is always uncertainty as to the diagnosis since definite proof of the diagnosis requires pathologic examination

Diagnosis

The clinical diagnosis should be suspected when congestive heart failure occurs in a person without evidence of congenital valvular, hypertensive or coronary (atherosclerotic) heart disease and without a history of rheumatic fever or a preceding infection in whom no other known cause of cardiac disease can be discovered A rapidly fatal course is confirmatory evidence

The *treatment* is that of congestive heart failure and is symptomatic Corticosteroid hormones (e g prednisone) should be given a therapeutic trial[40]

IDIOPATHIC HYPERTPOPHY OF THE HEART

A variety of cases of cardiac hypertrophy of obscure origin have been classified under the heading of idiopathic cardiac hypertrophy As our knowledge has increased cases of so-called idiopathic cardiac hypertrophy have been separated from this category and assigned to definite causes such as hypertension congenital lesions (p 784) and glycogen cardiomegaly (p 786) Chronic severe anemia beriberi pulmonary lesions and congenital anomalies of the coronary arteries are among other causes of cardiac hypertrophy which have sometimes been overlooked in the past

Congenital Idiopathic Hypertrophy (p 784)

Idiopathic Cardiac Hypertrophy in Adults

There is a motley group of cases characterized by cardiac hypertrophy and eventually by progressive congestive heart failure not due to any of the known causes of cardiac disease or cardiac hypertrophy[11] These are presently classified as idiopathic cardiac hypertrophy There are many resemblances to some of the cases described under congenital cardiac hypertrophy (p 784) but these cases occurring in adults are not regarded as of congenital origin They differ from the cases of idiopathic myocarditis with hypertrophy by the absence of inflammatory changes except focal reactions to necrotic muscle (See also glycogen storage disease of the heart p 786)

Pathology The outstanding pathologic finding is cardiac hypertrophy, but mural thrombi in either or both ventricles endocardial fibrosis degenerative necrotic and fibrotic myocardial changes are frequent associated findings In addition pulmonary emboli and infarcts and visceral congestion due to heart failure are commonly observed Cases of this type have been described under varying headings depending on the outstanding feature e g, cardiac hypertrophy of uncertain etiology in young adults,[67, 93, 28] myocardial hypertrophy of unknown etiology associated with congestive heart failure,[54] myocardial disease of obscure origin[100, 19] fibrosis of the endocardium and the myocardium with mural thrombosis[94] cardiovascular collagenosis with parietal endocardial fibrosis[8] Some of these cases appear to represent an adult form of endocardial fibroelastosis (p 637)

Etiology As indicated, the etiology is unknown The disease has been attributed in some cases to thiamine deficiency, i e, it has been interpreted as a form of beriberi heart[94] but the nutritional history, the high cardiac output the associated neurologic features and the response to thiamine administration seen in beriberi heart disease are not observed in idiopathic cardiac hypertrophy Idiopathic hypertrophy in this country presents many of the features of a common disease in Africans kwashiorkor (p 1037) thought to be due to malnutrition and/or vitamin deficiency[9, 49, 4]

Clinical Features The cases of idiopathic hypertrophy that I have observed concerned young or middle aged adults usually Negroes The outstanding clinical features were cardiac enlargement progressive and usually intractable heart failure and pulmonary embolization

Diagnosis The diagnosis was suggested by the inability to find evidence of the usual forms of heart disease in a patient with a very large heart and relatively recent and intractable heart failure There was no history of hypertension, the systolic blood pressure was relatively low and the pulse pressure often considerably reduced In other cases there was

a tendency to diagnose coronary heart disease but there was no history of angina pectoris or myocardial infarction and no distinctive electrocardiographic changes to suggest previous *myocardial infarction* In younger adults rheumatic heart disease was usually suggested and sometimes this was supported by the presence of a systolic murmur But there was neither history of a previous cardiac murmur nor evidence of the usual distinctive lesions of rheumatic valvular disease and the cardiac configuration was not that of mitral insufficiency In the absence of these or other distinctive types of cardiac disease idiopathic hypertrophy was suggested In the group of 9 cases reported by Davies et al [19] the problem was one of differentiation from pericardial disease because of the marked cardiac enlargement low pulse pressure paradoxical pulse and distant heart sounds Palpitation associated with arrhythmias was a major complaint in 2 cases and left bundle branch block was present in 4

In cases of congestive heart failure and cardiomegaly without apparent cause one must consider a variety of causes before a diagnosis of idiopathic hypertrophy is made viz hyperthyroidism periarteritis nodosa scleroderma amyloidosis sarcoidosis lupus erythematosus hemochromatosis myocarditis neoplasm

Levy and von Glahn[55] reported 10 instances in young adults of cardiac hypertrophy of unknown etiology In all there were symptoms of cardiac failure The heart sounds were weak and gallop rhythm was frequently present There were no murmurs of valvular disease In some there was electrocardiographic evidence of myocardial damage *and arrhythmias Infarction of the lungs* kidneys or spleen was frequent Death was due to progressive or recurrent cardiac failure in 7 patients and occurred suddenly in 3 At necropsy there was striking cardiac hypertrophy the average heart weight being 563 gm There was no significant coronary artery disease *or arteriolar sclerosis In 4 cases* microscopic examination of the heart revealed only hypertrophy in 2 a slight increase in connective tissue but in the remaining 4 there was extensive scarring with or without recent necrosis There were mural thrombi in six of the hearts In the cases of Flynn and Mann[26] which were characterized by endocardial and subendocardial degeneration mural thrombi and heart failure were associated with well known etiologic causes of heart disease In 8 cases of cardiac hypertrophy of obscure cause reported by Ware and Chapman [101] there was a chronic fibroplastic myocarditis characterized by extensive replacement of myocardial fibers by fibrous tissue Norris and Pote[76] reported 4 fatal cases of heart failure associated with unexplained hypertrophy of the heart in young men *Evans[23] described a familial type of cardiomegaly* in young adults not unlike the cases described by Levy and von Glahn Three similar cases of familial cardiomegaly were reported by Gaunt and Lecutier [30] In 10 *cases from the postmortem files of* The Mount Sinai Hospital New York [4] there were 7 *males and 3 females with ages ranging from 24* to 53 The clinical course was characterized by right and left sided heart failure with cardiomegaly and hepatomegaly in all pulmonary infarction with hemoptysis in 6 hydrothorax in 6 gallop rhythm in 6 and loud systolic murmurs in 4

Right Cardiac Hypertrophy and Endocardial Thrombosis of Obscure Origin (Primary Pulmonary Hypertension?)

Recent interest has been attracted to cases of idiopathic hypertrophy confined to or affecting *predominantly the right cardiac* chambers All known causes of right cardiac hypertrophy had been excluded in these cases by both clinical and microscopic examination Reports of cases of idiopathic hypertrophy of the right heart have been made by Oppenheimer [78] de Navasquez et al East [4] Armstrong[2] and Rosenbaum[81] *among others* The patients were predominantly females of all ages There was a *history of progressive* dyspnea later associated with cough cyanosis and advanced right sided heart failure In some cases there was a systolic pulsation and a systolic murmur over the pulmonic area and an accentuated second pulmonic sound *Roentgenologic examination* disclosed dilatation *of the pulmonary arteries and right* ventricular enlargement The *electrocardiogram* disclosed evidence of right ventricular strain and in some instances right atrial enlargement and right bundle branch block In almost all cases death occurred from congestive heart failure At autopsy there was predominant *or isolated hypertrophy of the right atrium*

chronic course lasting months or years. Idiopathic isolated myocarditis with progressive fatal course but of subacute or chronic duration has also been reported by Boikan[13] and by Franz.[37] About 15 per cent of the patients die suddenly,[41] the clinical picture being that of acute cardiac failure with pulmonary edema. When an occasional patient is said to have survived, there is always uncertainty as to the diagnosis, since definite proof of the diagnosis requires pathologic examination.

Diagnosis

The clinical diagnosis should be suspected when congestive heart failure occurs in a person without evidence of congenital, valvular, hypertensive or coronary (atherosclerotic) heart disease and without a history of rheumatic fever or a preceding infection, in whom no other known cause of cardiac disease can be discovered. A rapidly fatal course is confirmatory evidence.

The *treatment* is that of congestive heart failure and is symptomatic. Corticosteroid hormones (e.g., prednisone) should be given a therapeutic trial.[83]

IDIOPATHIC HYPERTPOPHY OF THE HEART

A variety of cases of cardiac hypertrophy of obscure origin have been classified under the heading of idiopathic cardiac hypertrophy. As our knowledge has increased, cases of so-called idiopathic cardiac hypertrophy have been separated from this category and assigned to definite causes such as hypertension, congenital lesions (p. 784) and glycogen cardiomegaly (p. 786). Chronic severe anemia, beriberi, pulmonary lesions and congenital anomalies of the coronary arteries are among other causes of cardiac hypertrophy which have sometimes been overlooked in the past.

Congenital Idiopathic Hypertrophy (p. 784)

Idiopathic Cardiac Hypertrophy in Adults

There is a motley group of cases characterized by cardiac hypertrophy and eventually by progressive congestive heart failure not due to any of the known causes of cardiac disease or cardiac hypertrophy.[91] These are presently classified as idiopathic cardiac hypertrophy. There are many resemblances to some of the cases described under congenital cardiac hypertrophy (p. 784), but these cases occurring in adults are not regarded as of congenital origin. They differ from the cases of idiopathic myocarditis with hypertrophy by the absence of inflammatory changes except focal reactions to necrotic muscle. (See also glycogen storage disease of the heart, p. 786.)

Pathology. The outstanding pathologic finding is cardiac hypertrophy, but mural thrombi in either or both ventricles, endocardial fibrosis, degenerative, necrotic and fibrotic myocardial changes are frequent associated findings. In addition, pulmonary emboli and infarcts and visceral congestion due to heart failure are commonly observed. Cases of this type have been described under varying headings depending on the outstanding feature, e.g., cardiac hypertrophy of uncertain etiology in young adults,[4, 93] myocardial hypertrophy of unknown etiology associated with congestive heart failure,[8] myocardial disease of obscure origin,[109, 11] fibrosis of the endocardium and the myocardium with mural thrombosis,[94] cardiovascular collagenosis with parietal endocardial fibrosis.[5] Some of these cases appear to represent an adult form of endocardial fibroelastosis (p. 637).

Etiology. As indicated, the etiology is unknown. The disease has been attributed in some cases to thiamine deficiency, i.e., it has been interpreted as a form of beriberi heart,[98] but the nutritional history, the high cardiac output, the associated neurologic features and the response to thiamine administration seen in beriberi heart disease are not observed in idiopathic cardiac hypertrophy. Idiopathic hypertrophy in this country presents many of the features of a common disease in Africans, kwashiorkor (p. 1037), thought to be due to malnutrition and/or vitamin deficiency.[2, 43, 4]

Clinical Features. The cases of idiopathic hypertrophy that I have observed concerned young or middle-aged adults, usually Negroes. The outstanding clinical features were cardiac enlargement, progressive and usually intractable heart failure, and pulmonary embolization.

Diagnosis. The diagnosis was suggested by the inability to find evidence of the usual forms of heart disease in a patient with a very large heart and relatively recent and intractable heart failure. There was no history of hypertension, the systolic blood pressure was relatively low and the pulse pressure often considerably reduced. In other cases there was

be subcutaneous edema hydrothorax and ascites Loss of ventricular distensibility with consequent limitation in diastolic volume may lead to hemodynamic disturbances and clinical features similar to those of constrictive pericarditis[45, 70]

The *electrocardiogram* usually discloses abnormalities but none that are specific for amyloidosis The most frequent changes include atrial fibrillation low voltage of the QRS and T waves and prolongation of the P R interval or complete atrioventricular dissociation[105, 33] QS complexes in right precordial leads suggestive of old anteroseptal infarction and electrical alternation of the *P waves were observed in one case of cardiac* amyloidosis[9b]

Pathologically the amyloid forms grayish nodules or diffuse thickening which causes a leathery rigidity and enlargement of the walls of the ventricles and atria[11] Frequently the amyloid affects the valves and may produce nodules and rigid thickening which interfere with valvular function[98] The coronary arteries as well as smaller vessels may be affected occasionally amyloid infiltration contributes to the coronary narrowing

Congestive heart failure is due chiefly and *most commonly to extensive myocardial in*volvement by amyloid which compresses and damages the muscle fibers and interferes with contraction and relaxation However coronary artery involvement with narrowing of these vessels valvular infiltration with consequent insufficiency and stenosis or extreme infiltration and narrowing of the small pulmonary arteries with secondary chronic cor pulmonale[33] are among occasional causes of congestive heart failure in primary amyloidosis

The *diagnosis* of amyloid disease of the *heart is to be considered in the presence of* cardiac enlargement or heart failure without apparent cause A supporting clue may be found in associated amyloid deposits proven by biopsy e g in the skin simulating scleroderma in the tongue causing macroglossia or tumor formation in the muscle simulating myotonia or occasionally in the *tissues about the joints larynx and other* sites or in the presence of multiple myeloma A Congo red test may be helpful but this may be negative in the primary type of amyloidosis in which the liver is not involved Gum biopsies frequently disclose the presence of amyloid In a patient known to have amyloidosis but none of the common cardiac diseases the presence of low voltage of QRS and T conduction disturbance or atrial fibrillation suggests cardiac involvement by the amyloid

Treatment of primary amyloidosis involving the heart is unsatisfactory In the presence of congestive heart failure the usual therapeutic measures should be employed (p 234)

SARCOIDOSIS

Sarcoidosis is a chronic granulomatous disease whose lesions resemble those of noncaseating tuberculosis but is usually as*sociated with a negative tuberculin reaction* It may affect the heart by causing right heart strain secondary to extensive pulmonary involvement (p 978) or rarely by direct myocardial involvement

Sarcoidosis produces yellowish circumscribed or diffuse tumor like infiltrations of the heart which consist of granulomata containing very large giant cells as well as epithelioid and plasma cells and lymphocytes but no polymorphonuclear leukocytes Diffuse extensive fibrosis may predominate over scattered giant cell granulomata[1] Myocardial damage may be caused by *the active granulo*mata or by subsequent scarring and replacement of muscle fibers

Sarcoidosis of the myocardium may be asymptomatic but congestive heart failure is not unusual[62] In 6 of a series of 31 patients studied by Longcope and Fisher[63] there was evidence of myocardial insufficiency during life or sarcoidosis of the heart was discovered at autopsy In 5 of the cases with heart failure there were also enlargement of the heart arrhythmia and electrocardiographic changes In the cases reported by Bates and Walsh[7] *there was extensive myocardial sarcoidosis* but tachycardia was the only clinical symptom Sudden death may occur[98]

Electrocardiographic abnormalities[62, 88] consist of prolonged P R interval bundle branch block prolonged QRS ST segment depressions flat or inverted T waves and occasional prominent P waves

The *diagnosis* of cardiac sarcoidosis is suggested by heart failure of obscure origin in a patient proven to have sarcoidosis (lymph node biopsy positive Nickerson Kveim test) but with insufficient pulmonary lesions to account for the heart failure

LUPUS ERYTHEMATOSUS (See p 633)

Although the epicardium and endocardium are most strikingly involved the myocardium also contains microscopic lesions in many cases[11] The lesions consist of fibrinoid necrosis of the supporting structures and of the blood vessels with secondary myocardial degeneration and fibrosis Occasionally there is a clinical picture of angina pectoris and there may be electrocardiographic changes simulating acute myocardial infarction[99] More commonly there are non specific T wave changes and changing P R interval or RS T and T wave changes due to an associated pericarditis Congestive heart failure may occur in one quarter of the cases of lupus erythematosus[3] but usually only toward the end of the clinical course Gallop rhythm occurs commonly before there is overt evidence of congestive heart failure

NECROTIZING ANGIITIS

Myocardial lesions occur in periarteritis nodosa and in related forms of necrotizing angiitis Myocardial infarction secondary to necrotizing arteritis of the coronary arteries has been mentioned (p 440) Cardiac enlargement and heart failure may be secondary to severe or malignant hypertension which occurs in many cases of periarteritis nodosa Necrotizing angiitis (hypersensitivity angiitis) with involvement of the small coronary vessels and secondary miliary infarcts may result from the administration of drugs or foreign proteins The occurrence of another variant allergic granulomatous angiitis with giant cell granulomatous myocarditis has been mentioned (p 620)

MYOTONIA ATROPHICA

This is a familial disease characterized by increased muscle tone atrophy of muscles (face neck, thigh forearm hand), dimpling of tongue when the lower teeth are struck by a hammer cataract formation premature baldness, testicular atrophy and impotence It may represent a later stage of myotonia congenita of Oppenheim[88]

Maas and Zondek[67] first called attention to cardiac involvement in this disease Mondon and Pasquet[73] and Romano and Michael[80] emphasized the frequency of cardiovascular abnormalities especially coronary atherosclerosis but the electrocardiographic abnormalities to be described are probably not due to coincident coronary disease[3] Evans[7] described the cardiac findings in 13 cases of myotonia atrophica The electrocardiogram disclosed a prolonged P R interval, low voltage of the P waves slurring of the QRS left axis deviation and bundle branch block In two cases there were breathlessness and cardiac enlargement but no other signs of heart failure Atrioventricular dissociation with Adams-Stokes syndrome has been described[6] Conduction defects and cardiac arrhythmias are the commonest electrocardiographic abnormalities[85] The first sound at the apex may be split In other cases bradycardia hypotension, depression of ST segments and inversion of T waves with little or no cardiac enlargement have been noted[79] In the case studied by Black and Ravin[1] the R T segment was elevated in leads I and II There may be a triple rhythm Quinine may afford some relief to the myotonia, but does not alter the progress of the disease

FRIEDREICH'S ATAXIA

Attention has been called in the French and British literature to the finding of cardiac lesions and electrocardiographic changes in individuals suffering from Friedreich's hereditary ataxia Russell[83] and Manning[65] described pronounced cardiac hypertrophy, fatty and eosinophilic degeneration and lymphocytic interstitial myocarditis in children and young adults with Friedreich's disease some of whom died of heart failure Evans and Wright[28] observed complete heart block and bundle branch block or RS-T and T wave changes resembling those seen in cases of myocardial infarction Lorenz et al[64] described the cases of 5 siblings with similar cardiac findings Angina pectoris has been reported[97]

PROGRESSIVE MUSCULAR DYSTROPHY

Myocardial fibrosis and mild degenerative and inflammatory changes somewhat similar to those in the skeletal muscle have been observed in the hearts of individuals with progressive muscular dystrophy[10, 77] There is usually an increase in fatty and fibrous tissue with hypertrophy or atrophy of the myocardial fibers and vacuolar and other degenerative changes in these fibers[98] The incidence of cardiac involvement has been reported to vary between 50 and 85 per cent[9]

In many cases tachycardia arrhythmia or heart failure had been present [82, 85, 78] Sudden death may occur [3] There may be a shortening of the P R interval and abnomal Q waves P wave abnormalities are frequent The occurrence of electrocardiographic changes in a case of progressive muscular dystrophy suggests involvement of the heart by the same histologic changes found in the skeletal muscle [103] However according to Grandell [43] dystrophic myocardial involvement is uncommon in progressive muscular dystrophy and electrocardiographic and ballistocardiographic abnormalities are usually due to other causes

GARGOYLISM (LIPOCHONDRODYSTROPHY)

This is a rare generalized storage disease of infancy and childhood characterized by the deposition of a macromolecular glycoprotein In the majority of autopsies in gargoylism there is gross or microscopic evidence of cardiovascular disease [80] There is diffuse involvement of the myocardial connective tissue especially that of the valves and coronary arteries Cardiac failure is the common cause of death [58]

FATTY INFILTRATION OF THE HEART (FATTY HEART LIPOMATOSIS CORDIS)

Fatty heart denotes an excessive deposition (infiltration) of normal fat chiefly in the subepicardium of the anterior wall of the right ventricle with extension into and replacement of the subjacent myocardium Occasionally the left ventricle atria and bundle of His may be involved Fatty heart occurs in the markedly obese and was said to occur in heavy beer drinkers Occasionally clinical heart disease e g angina pectoris is found in the absence of any significant cardiac finding except severe fatty infiltration [13]

ATROPHY OF THE HEART

Atrophy of the heart[47] denotes an acquired reduction in size and weight of the heart This occurs with inanition particularly in association with malignant neoplasms and chronic infections In addition to its small size and diminished weight the heart is characterized by increased pigmentation of the muscle fibers decreased size of the fibers with a relative increase in the nuclei wrinkling of the pericardium with serous atrophy of the subepicardial fat and tortuosity of the coronary arteries Although apical systolic murmurs are frequently associated and the electrocardiogram may show low voltage of the QRS complex and T wave and prolongation of the P R and Q T intervals the atrophic heart is competent for the needs of the individual concerned Atrophy of the heart is a reversible pathologic change not a clinical disease

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Chapter 25

ENDOCARDITIS AND ENDOCARDIAL DISEASE

DEFINITION

Endocarditis in its narrowest sense refers to exudative and proliferative inflammatory alterations of the inner lining of the heart. The term was first introduced by Bouillaud.[4] Sometimes the term endocarditis is applied rather loosely to a number of simple thrombotic or degenerative lesions of the endocardium. *Endocarditis most frequently involves* the valvular endocardium but it may also affect the inner lining of the cardiac chambers (parietal or mural endocarditis) or the endocardium of the chordae tendineae papillary muscles or trabeculae carneae.

CLASSIFICATION

Endocarditis is merely a general pathologic anatomic diagnosis which does not reveal the different etiologic factors concerned. A complete diagnosis should also include the causative bacterial agent or the general disease of which the endocarditis is a part. According to the studies of Libman[35] and of Friedberg and Gross[15] endocarditis may be classified as

1. Acute and subacute bacterial endocarditis
2. Rheumatic endocarditis
3. Atypical verrucous endocarditis of Libman Sacks disease (lupus erythematosus)
4. Non bacterial thrombotic endocarditis (terminal or cachectic endocarditis thromboendocarditis or non bacterial thrombosis of the endocardium)
5. Syphilitic endocarditis
6. Tuberculous endocarditis
7. Unclassified

In addition there are a number of degenerative alterations of the endocardium which may be primary or superimposed on a pre existing endocarditis. These degenerative changes include endocardial fibroelastosis or sclerosis calcification or rarely ossification fatty degeneration mucoid softening and amyloidosis.

Endocarditis may be one element of a more extensive cardiac disease in which the myocardium pericardium or both are simultaneously involved. Sometimes the endocarditis is only one feature of a generalized disease in which it may be the primary factor determining the clinical picture or merely a secondary element with or without significant *clinical manifestations. For these reasons the* main forms of endocarditis such as the bacterial and rheumatic are discussed separately and in detail in connection with etiologic diseases of which they are a part. Syphilitic and tuberculous endocarditis are rare and unimportant and are considered briefly in connection with other syphilitic and tuberculous lesions of the heart. The purpose of this chapter is to provide an orientation to the different forms of endocarditis.

It is important to distinguish endocarditis itself from the end results or complications of endocarditis. The latter include valvular defects and emboli. Valvular defects arise because of the thickening shortening fixation and deformity of the cusps and chordae tendineae resulting from organization fibrosis contraction and adhesions which represent healing of the inflammatory process. These by preventing proper apposition opening and closing of the valve cusps produce valvular stenosis or insufficiency. Emboli result from the detachment of particles of friable verrucae (usually containing bacteria) or of parietal endocardial thrombi which may develop at the site of parietal endocarditis. The formation of atrial or ventricular mural thrombi is facilitated by the presence of endocarditis at the sites involved.

GENERAL PATHOLOGY OF ENDOCARDITIS

The pathology of endocarditis is characterized by the presence of verrucae on the surface of the endocardium and by changes in the endocardium itself.

1 Verrucae

Superficial excrescences or vegetations termed *verrucae* (Laennec) situated usually on the surface of the valvular endocardium but occasionally also on the parietal endocardium, constitute the most obvious feature of endocarditis The examination of slides containing stained crushings of the verrucae divides the endocarditides into two major groups the bacterial and the non bacterial The vegetations of bacterial endocarditis reveal *numerous* organisms in such spreads except in the healed stages Cultures from the vegetations may help to identify the causative organism but postmortem cultures are not always reliable [14] If there are no bacteria in the vegetations they are due to rheumatic endocarditis healed bacterial endocarditis atypical verrucous endocarditis (Libman Sacks disease) or non bacterial thrombotic endocarditis

The *size of the vegetation* is not a reliable means of differentiating the various forms of endocarditis Minute yellowish soft vegetations about 0 5 to 2 mm in diameter situated in beadlike fashion along the closure line of the cusps are usually rheumatic But terminal acute bacterial endocarditis or terminal non-bacterial thrombotic endocarditis may produce vegetations of similar size and location Usually the bacterial vegetations are larger than the rheumatic averaging about 5 mm in size When multiple they may be as small as 1 or 2 mm, while occasionally there are isolated vegetations 1 to 2 cm in diameter or even larger The non bacterial thrombotic verrucae may be as small as the usual rheumatic vegetation or may form larger conglomerate masses or stalked polyps The huge irregular ulcerated or purulent cauliflower vegetations which are occasionally observed generally represent acute bacterial endocarditis Sometimes the bacterial vegetations are greatly enlarged by the accretion of currant jelly clot to their ulcerated surface When situated on the mitral valvular endocardium they may enhance or produce a mitral stenosis or act as a ball valve thrombus to occlude completely the mitral orifice The vegetations in atypical verrucous endocarditis may be indistinguishable in size from rheumatic verrucae they may form massive conglomerate lesions or they may be of the flat spreading variety which covers a considerable portion of the valvular surface

The *location and distribution* of the vegetations may be diagnostically suggestive Definite elevated verrucae on the posterior wall of the left ventricle are usually bacterial, mostly of the subacute variety The presence of mural endocardial lesions (except minute ones in the left atrium) practically excludes a rheumatic etiology and suggests bacterial endocarditis or atypical verrucous endocarditis Verrucae situated exclusively or chiefly on the tricuspid leaflets without simultaneous lesions on the aortic leaflet usually represent atypical verrucous or bacterial endocarditis Verrucae which are situated only or predominantly in the pockets of the atrioventricular valves and the adjacent ventricular myocardium are almost always due to atypical verrucous endocarditis Vegetations which are associated with ulceration and aneurysm of the cusps and rupture of the chordae tendineae are bacterial in origin If there is complete perforation of a cusp it is more likely due to acute than to subacute bacterial endocarditis The non bacterial thrombotic vegetations, like the rheumatic, are limited essentially to the atrial surface of the atrioventricular cusp and to the ventricular surface of the semilunar cusps they affect the mitral aortic tricuspid and pulmonic valves in that order of frequency individually or in combination

Bacterial vegetations may occur simultaneously with non bacterial vegetations in the same heart and even on the same cusps Thus subacute bacterial endocarditis is frequently superimposed on an active rheumatic endocarditis and an acute terminal bacterial endocarditis is a common complication of the atypical verrucous endocarditis of Libman Sacks disease (disseminated lupus erythematosus)

2 Changes in the Endocardial Substance

The inflammatory changes in the endocardium itself are often the essential feature of endocarditis although their macroscopic appearance is less striking than that of the verrucae Valvular endocarditis especially in rheumatic fever, but occasionally also in Libman Sacks disease, may occur without the formation of verrucae Even when verrucae are present on one or more of the valves a valvulitis without verrucae may be found on the others An atrial endocarditis is almost always found in association with acute rheumatic heart disease but overlying ver

rucae are usually absent or barely visible

The most intense inflammatory reaction is found in rheumatic endocarditis (see below) Beginning in the ring of the cusp it extends a short way or more often to the closure line or tip The inflammatory reaction is both proliferative and exudative the valve is vascularized and organization occurs early Necrosis is absent On the other hand, in the acute bacterial endocarditis valvular necrosis is a prominent feature while inflammatory reaction is scant except for polymorphonuclear leukocytes within the vegetation and in the immediate vicinity of necrotic areas Subacute bacterial endocarditis produces a lesser degree of necrosis and a greater degree of inflammatory reaction the latter being characterized by the infiltration and proliferation of mononuclear cells The valves in atypical verrucous endocarditis may or may not suffer some necrosis An inflammatory reaction tends to be located near both surfaces of the cusps and near the pocket of the valve Plasma cells large mononuclear cells and endothelial bud capillaries are prominent features In nonbacterial *thrombotic endocarditis* the cusps are strikingly free from acute inflammatory change but in most instances they are thickened and deformed by considerable fibrous tissue representing chronic healed rheumatic endocarditis

General Pathogenesis of Endocarditis

The etiology and pathogenesis of endocarditis are discussed in connection with the individual forms of endocarditis

CHARACTERIZATION OF INDIVIDUAL FORMS OF ENDOCARDITIS

Bacterial Endocarditis (Chapter 34)
Rheumatic Endocarditis (Chapters 31–33)

ATYPICAL VERRUCOUS ENDOCARDITIS (LIBMAN SACKS DISEASE) (ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS)

This is a form of endocarditis with nonbacterial verrucae which are usually macroscopically different from rheumatic verrucae and which were first described in 4 cases of a fatal febrile disease reported by Libman and Sacks[36] The latter is a clinical pathologic entity which is now generally termed acute disseminated *lupus erythematosus*[35] The endocardial verrucae are frequently absent and are not significant for the clinical picture[14] Endocardial lesions were found by Humphreys[27] in 12 of 21 cases of acute disseminated lupus erythematosus Like rheumatic endocarditis atypical verrucous endocarditis is only one part of a general febrile disease in which blood cultures are negative and in which serous membranes the skin the blood vessels and other structures may be affected But unlike rheumatic fever the cardiac lesions including the endocarditis, are usually clinically unimportant except toward the end of the clinical course

Etiology

The cause of the disease *is unknown A remarkable* feature is its predominant occurrence in young women of childbearing age Like periarteritis nodosa and rheumatic fever Libman-Sacks disease has been interpreted as an allergic (hypersensitive) tissue reaction chiefly on the basis of the pathologic findings[40] [45] However there is no definite clinical evidence to support this interpretation[2] although several cases have appeared among student nurses following the injection of Dick toxin[1] Lupus erythematosus is classified as a collagen disease[20] [3] [18] *a misnomer* which is difficult to dislodge because it provides a useful catchbasket for a variety of diseases of unknown etiology

Endocardial Lesions

The verrucae are usually *broader and more* massive than in rheumatic endocarditis and have a great tendency to involve the mural endocardium the endocardium of the valve pockets both sides of the cusps and the right side of the heart[11] The tricuspid valve is more often affected than the mitral and the pulmonic more often than the aortic The verrucae consist of areas of proliferating and degenerated valve substance mixed with fibrin and platelet thrombi The cusps contain large mononuclear and plasma cells macrophages fibroblasts capillaries of the endothelial bud type and necrotic cells forming characteristic *hematoxylin stained bodies*[19] These are believed to represent the histologic analogue of the lupus erythematosus cells (L E cells)[22] [a] [14] *found in the bone marrow* and blood Histochemical studies indicate that the hematoxylin stained bodies (blue-cell lesions) represent depolymerized desoxyribosenucleic acids formed by the *necrosis of cell nuclei*[31] Not uncommonly there is a terminal bacterial invasion of the blood stream with the production of an acute bacterial endocarditis A nonbacterial ter

minal thrombotic endocarditis (see below) may also be associated with atypical verrucous endocarditis or it may occur as the only macroscopic endocardial lesion in Libman Sacks disease

Myocardial Lesions

In the myocardium the lesions include foci of round cells atrophy of fat or interstitial edema fibrinoid necrosis, thickening and stenosis of small arteries and fine scars suggestive of small infarcts Aschoff bodies are absent The heart is usually of normal size but may be slightly hypertrophied The visible myocardial lesions do not appear sufficient to account for the frequent occurrence of heart failure in advanced stages of the disease

Pericardial Lesions

Adhesive pericarditis is frequent and a serofibrinous pericarditis is not uncommon In 5 of the 21 cases analyzed by Humphreys[7] there were effusions of 600 to 950 cc

The changes in the heart appear to be part of a widespread alteration of the ground substance[8, 80] The serous membranes vasculature (especially the glomerular capillaries) lymph node skin and mediastinal and retroperitoneal areas are affected Fibrinoid metamorphosis and fragmentation of collagen swelling and increased density of the interfibrillar ground substance wire-loop lesions and focal necrosis of the glomerular capillaries sclerosis of the collagen fibers around the follicular arteries of the spleen and the endocardial lesions are the most conspicuous diagnostic features Although similarities to periarteritis nodosa rheumatic fever and scleroderma have been stressed the pathologic and clinical features of each are usually easily distinguishable Some confusion has arisen because Libman Sacks disease may be associated with necrotizing arteritis or occasionally with scleroderma

Clinical Features[4, 5, 41]

Although Libman Sacks disease is not usually a clinical cardiac ailment its chief clinical features merit brief discussion because it is often confused with rheumatic fever or bacterial endocarditis

Fever is an essential feature The onset is usually characterized by diffuse arthralgias and stiffness of the small and large joints of the extremities Occasionally there are joint changes resembling those of rheumatoid arthritis Not infrequently the patient is first treated for arthritis for which he goes to the seashore where exposure to the sun is followed by distinctive cutaneous lesions However, the onset may be characterized by a 'butterfly' or other eruption, by Raynaud's phenomenon hemolytic anemia, thrombocytopenic purpura, pleurisy or pericarditis[11]

The acute disseminated lesions of lupus erythematosus are most often suggestive of the diagnosis but these lesions may be absent or develop late in the disease The lesions consist of a characteristic, slightly raised erythematous butterfly eruption across the bridge of the nose and extending to the cheeks Papular and erythematous lesions of a bluish red cast also affect other parts of the face, the forehead the ears the manubrium sterni the volar surface of the fingers the thenar and hypothenar eminences and other parts of the upper and lower extremities Telangiectatic and petechial lesions also occur The skin of the face may become scaly and edematous, and the lesion may resemble that of seborrheic dermatitis or erysipelas Erythematous or ulcerative lesions may appear on the hard palate or other parts of the oral mucosa

Albuminuria, microscopic hematuria or the presence of clumped leukocytes in the urine often appears early and may suggest a diagnosis of glomerulonephritis or pyelonephritis The fundi may disclose cotton wool 'exudates' (retinal cytoid bodies) but the blood pressure is almost always normal Fleeting or persistent pleuropneumonic lesions pleurisy with effusion which may be eosinophilic, or evidence of serofibrinous pericarditis is commonly observed Lymphadenopathy and splenomegaly, Raynaud like phenomena scleroderma and cerebral manifestations notably convulsions occur occasionally and evidence of impaired renal function bronchopneumonia and bacterial endocarditis appear late in the disease or preterminally The liver may be enlarged owing to fatty infiltration Dyspnea abdominal pain and chest pain are among the more common subjective symptoms, after fever and joint pains Ascites occurs eventually in about one quarter of the cases Renal insufficiency and uremia are common occurrences toward the end of the disease

Leukopenia anemia occasional thrombocytopenia a reduction in plasma albumin hyperglobulinemia (especially alpha 2 and

gamma globulins) and an occasional false positive Wassermann test[25] are additional features Thrombocytopenia purpura may be an early manifestation Splenectomy may then first reveal the typical onion skin lesions (periarterial fibrosis) of lupus erythematosus A severe hemolytic anemia occurs frequently Leukocytosis is common toward the end of the disease chiefly due to intercurrent infection

Clinical evidence of cardiac involvement is less striking than the pathologic changes in the heart Pericardial effusion and less commonly fibrinous pericarditis are the most frequent manifestations An apical systolic murmur may be audible in almost half the cases but this cannot be correlated with the verrucous endocardial lesions Clinical evidence of heart failure is common in the end stages of the disease Gallop rhythm is frequent under these circumstances The heart failure may be due to myocardial disease or may be secondary to pericardial effusion with cardiac tamponade Hypertension is unusual except in advanced stages of renal insufficiency with azotemia

The electrocardiogram discloses no characteristic changes but occasionally there may be low voltage of the QRS complexes an increased P R interval low or inverted T waves and a tendency to a prolonged Q T interval[32] There may be classic RT elevations characteristic of pericarditis

Diagnosis

Most often Libman Sacks disease is confused with rheumatic fever rheumatoid arthritis or subacute bacterial endocarditis but also with glomerulonephritis or pyelonephritis pleuropericarditis or rarely Hodgkin s disease if there is a prominent lymphadenopathy

The combination of fever arthralgia lupus erythematosus and leukopenia in a young woman is usually adequate for diagnosis The blood culture should be negative except in the terminal stage Rheumatic fever and periarteritis nodosa are associated with a polynuclear leukocytosis as a rule A definitive diagnosis is made by finding the L E cells in bone marrow or blood[27 28 ...] Rarely a positive L E finding is reported in other conditions

In the absence of characteristic cutaneous lesions Libman Sacks disease may be suspected in cases resembling rheumatic fever in which there is evidence of acute glomerulonephritis and azotemia but with a normal blood pressure Similarly the association of thrombocytopenic purpura or of leukopenia or both in cases resembling rheumatic fever should suggest Libman Sacks disease The combination of azotemia fever and normal blood pressure may also be due to this disease It has also masqueraded as a subacute polyserositis with fever with or without arthritis and glomerulonephritis[31] In cases resembling bacterial endocarditis but in which the blood cultures are persistently negative Libman Sacks disease should be suspected especially if there is no organic cardiac murmur

Treatment consists in administration of adrenocortical drugs[... ...] In acute episodes fever and associated symptoms may be best controlled by 100 units or more of corticotropin daily administered by slow intravenous drip As soon as the symptoms are controlled the patient is given 60 to 100 mg of oral prednisone daily in divided doses In milder cases control may be effected by oral medication from the beginning The dose is gradually and progressively reduced if the clinical response is maintained Frequently a prolonged maintenance dose of 15 to 20 mg of prednisone suffices Dubois[1] reported beneficial effects from the use of quinacrine (Atabrine) in the treatment of both systemic and discoid lupus erythematosus He administered 300 mg daily the first week and increased or diminished the dose according to the clinical response and the presence of toxicity Thoracentesis is occasionally required if there are respiratory symptoms due to large pleural effusions Salicylates may ameliorate the joint pains and fevers Transfusions are indicated if there is pronounced anemia and hypoproteinemia Penicillin or streptomycin may be required to control complicating infections Death usually occurs within a period of six months to two years but I have seen many patients who have thus far survived four years or longer

NON BACTERIAL THROMBOTIC ENDOCARDITIS

This refers to the verrucous endocardial lesions which are associated with a variety of infections and chronic wasting diseases The term cachectic endocarditis was applied by Harbitz[21] to these lesions but because they occur toward the end of the disease they have

also been classified as terminal endocarditis. Many of the lesions diagnosed as terminal endocarditis prove on careful bacteriologic and microscopic examination to be examples of active rheumatic verrucous endocarditis or terminal bacterial endocarditis.[9] The latter two forms should be distinguished from the cases under consideration. The term thromboendocarditis was introduced by Ziegler[54] to emphasize the essential thrombotic nature of the lesions. Koniger[32] in his extensive study of endocarditis referred to this group as simple thromboendocarditis. It is preferable to avoid this term which according to recent usage has come to be applied to all types of non-bacterial verrucous endocarditis including rheumatic endocarditis. Gross and Friedberg[9] introduced the term non bacterial thrombotic endocarditis to denote the essential descriptive features. But it is questionable whether the term endocarditis may be properly employed in these cases since there is little or no inflammatory reaction in the cusps. Perhaps non bacterial thrombosis of the endocardium would be a more accurate term although it is probable that the deposition of thrombus is secondary to a toxic damage to the cusp itself.[33, 9]

The essential feature in these cases is the presence of non-specific valvular vegetations which may resemble those of rheumatic endocarditis. Sometimes they are minute and arranged in rows on the closure line of the cusps. But they may be much larger than rheumatic verrucae and appear as a pyramidal ridge or a massive solitary sessile or pedunculated lesion. The mitral, aortic and tricuspid valves are affected in that order as in rheumatic endocarditis. Neither the mural endocardium nor the chordae are involved. Valvular deformities do not result from the lesions.

Microscopically the vegetations consist essentially of agglutinated blood platelet thrombi. Superficially there is a small or large cap of fresh thrombus often overlying an amorphous irregular area of valve substance which has undergone eosinophilic or fibrinoid degeneration. There are no bacteria in the vegetation. A striking feature which contrasts with the findings in active rheumatic endocarditis is the absence or paucity of inflammatory reaction in the cusp despite the freshness of the verrucous lesion. When cells are present they are usually fibroblasts and histiocytes which participate in early organization of the base of the verrucae. There are no Aschoff bodies in the heart. In a preponderant majority of cases the verrucous lesions are superimposed on thickened, fibrotic deformed valves usually the result of chronic rheumatic endocarditis.

Non bacterial endocarditis is an accidental occurrence in a variety of infections and chronic wasting diseases which, as a rule, has no clinical significance except that it may facilitate a superimposed bacterial endocarditis. However, the non bacterial vegetations give rise to systemic emboli especially to the brain.[7] The non bacterial verrucous lesions appear most often in association with carcinomatosis, glomerulonephritis, chronic pulmonary disease including tuberculosis, uremia, lobar pneumonia, leukemia, osteomyelitis, cirrhosis of the liver and Libman-Sacks disease. The possibility that metabolic or bacterial toxins may contribute to valvular injury and subsequent endocardial thrombosis has been mentioned. Previous valvular deformity by rheumatic endocarditis favors secondary deposition of non bacterial thrombi. Friedberg and Gross[13] observed 3 cases of non bacterial thrombotic endocarditis associated with fever, essential (thrombocytopenic) purpura hemorrhagica and vascular lesions (thrombotic thrombocytopenic purpura). The endocarditis was not related to the clinical picture. Friedberg, Gross and Wallach[14] also reported 4 cases of this form of endocarditis associated with prolonged fever, arthritis, inflammation of serous membranes and vascular lesions. The latter may now be classified as examples of Libman-Sacks disease (lupus erythematosus). The non specific non bacterial thrombotic endocarditis as well as the characteristic atypical verrucous endocarditis (and a terminal bacterial endocarditis) may occur in Libman Sacks disease.

SYPHILITIC ENDOCARDITIS

This is rarely if ever a primary endocarditis, but results from the contiguous spread of the syphilitic aortic lesion to the commissures and bases of the aortic cusps (p 895). Rarely the aortic leaflet of the mitral valve is involved by contiguous spread of syphilitic inflammation from the aorta.[47]

TUBERCULOUS ENDOCARDITIS

This occurs very rarely. The endocardium

may be involved by extension of a tuberculous perimyocarditis or by miliary tubercles in instances of generalized miliary tuberculosis (pp 602 and 913)

ENDOCARDIAL FIBROELASTOSIS LOEFFLER'S FIBROPLASTIC ENDOCARDITIS CONSTRICTIVE ENDOCARDITIS

A variety of cases of heart disease of unknown etiology are characterized pathologically by thickening of the endocardium One large group in which there is a prominent proliferation of endocardial and subendocardial fibrous and elastic tissue is termed endocardial fibroelastosis and less frequently endocardial fibrosis or sclerosis Endocardial fibroelastosis in the first two years of life is a congenital and possibly hereditary disease which is the commonest cause of congenital idiopathic cardiac hypertrophy (see p 786) In addition there are cases of fibroelastosis in childhood (ages 2 to 16) which are probably identical with those in the younger group except for the later age of onset[10]

Finally endocardial fibroelastosis of similar pathologic nature is encountered in adults[10, 11] in cases of idiopathic hypertrophy and heart failure (p 624) In these mural thrombosis with resultant emboli is a frequent finding There are case reports of endocardial fibroelastosis in patients aged 53 and 71 with cardiac symptoms for 6 and 15 years respectively[12] Despite the long interval between birth and the development of symptoms the adult form of endocardial fibroelastosis like the infantile may be congenital Since endocardial fibroelastosis is seen to varying extent in other conditions associated with cardiac hypertrophy and heart failure the fibroelastosis may be a non-specific reaction to some undetermined factor such as myocardial anoxia[23] or more probably to altered fetal pressure relations with increased tension in the affected chamber The clinical features of the adult cases of endocardial fibroelastosis are those described under the heading idiopathic cardiac hypertrophy (p 624) Congestive heart failure embolization conduction disturbances and cardiac arrhythmias and a syndrome resembling that of constrictive pericarditis are most frequently observed

The cases of heart disease occurring frequently in East Africans known as East African endomyocardial necrosis[17, 3] resemble clinically those of endocardial fibroelastosis with respect to the presence of congestive heart failure of undetermined origin But pathologically they differ distinctly in that (1) the patchy endocardial thickening shows only irregular masses of endocardial elastic tissue instead of proliferating elastic tissue and (2) the thickened areas show destruction of the original endocardium and adjacent myocardium with replacement by vascular fibrous tissue[20] Mitral or tricuspid insufficiency may occur The cases from South Africa described as cardiovascular collagenosis with parietal endocardial thrombosis[3] may be identical with East African endomyocardial necrosis A review of the various types of endocardial fibrosis indicated to Davies and Ball[8] that virus infection some antigen antibody reaction and malnutrition were the possible etiologic factors in the endocardial fibrosis observed in Uganda The clinical picture is dominated by progressive congestive heart failure and death is due to the heart failure bacterial endocarditis or intercurrent infection[3]

Certain inflammatory lesions of the endocardium still cannot be accurately classified Among these are the cases of isolated parietal endocarditis such as those reported by Baumler[4] and by Loeffler[31] Baumler described an extensive whitening and thickening of the left ventricular endocardium especially near its apex associated with mural thrombi and cardiac dilatation but without valvular lesions The patients suffered from chronic congestive cardiac failure especially from attacks of nocturnal dyspnea and sometimes from an anginal syndrome The resemblance to some of the cases of idiopathic hypertrophy and heart failure is noted

Loeffler[31] reported 2 cases of an afebrile parietal fibroplastic endocarditis of both ventricles There was an insignificant mitral valvulitis and insufficiency The clinical picture which resembled that of constrictive pericarditis was characterized by persistent tachycardia progressive evidences of visceral congestion including enlargement of liver and spleen serous effusions in the pleural cavity subcutaneous edema of the lower extremities and finally ascites and edema of the upper extremities The clinical manifestations were attributed to interference of the thickened retracted endocardium with the inflow of

blood into the right ventricle A remarkable feature was the presence of an eosinophilia which in one case reached 70 per cent with a leukocytosis of 18 000 Hoffman et al[26] reported a case of Loeffler s fibroplastic endocarditis with eosinophilia and reviewed the literature

Cases pathologically similar to Loeffler s endocarditis parietalis have been described under the heading of *constrictive endocarditis*[39] or constrictive endocardial sclerosis because the thickened endocardium was thought to restrict the diastolic expansion and perhaps the systolic contraction of the ventricles The clinical picture was precisely that of constrictive pericarditis (p 611) Cases of 'recurrent parietal thromboendocarditis simulating coronary disease and associated with hypotension and disturbances in cardiac rhythm have been observed in young adults[40]

OTHER ENDOCARDIAL LESIONS

A number of non inflammatory and degenerative endocardial lesions especially of the valves must not be confused with endocarditis Certain hair like *endocardial tags* such as the Lamblian excrescences from the nodulus aurantii may occasionally simulate endocardial vegetations[18] They are composed of myxomatous or hyaline connective tissue without thrombus or associated valvular inflammation

Yellow flecks or plaques of *atheromatous degeneration* are common on the ventricular surface of the anterior (aortic) cusp of the mitral valve They are most frequent and prominent in the hearts of elderly and anemic subjects They consist of collections of lipoid material sometimes with calcium

Valvular sclerosis is common There may be only whitish plaques of valvular thickening occupying the distal portion of the leaflets especially of the mitral valve They consist of fibrous tissue The atheromatous areas in the anterior mitral cusp may undergo fibrous replacement or occasionally calcification These changes do not interfere with valvular function for they are not extensive Occasionally the ring of the mitral or aortic valve or both is infiltrated by a rigid incomplete collar of calcium (sclerosis annularis fibrosi—Dewitzky[10]) Ossification may occur Calcification of the mitral or aortic ring may be denoted clinically by the presence of a loud very harsh or musical systolic murmur Histologically there is evidence that extensive fibrosis, hyalinization and occasionally elastification precede the deposition of calcium

Calcification of valve cusps occurs usually when there is longstanding chronic rheumatic endocarditis But occasionally calcification and consequent stenosis of the aortic valve may occur as a primary degenerative process[43 17] (p 698) In these cases fibrosis and calcification begin in the arterial portion of the aortic valve near its base and extend from there to the sinuses of Valsalva (Monckeberg's ascending sclerosis) or up the aortic leaflets until the whole valve is a hard, rigid mass with irregular calcific nodules and spicules which penetrate the ventricular surface (p 698) In the fully developed stage it is indistinguishable from the much more common calcific aortic stenosis of rheumatic origin The roentgenologic diagnosis of calcification of the annulus fibrosus, mitral and aortic cusps is discussed elsewhere (p 704)

Endocardial pockets also known as accessory leaflets regurgitant pockets or birds' nests are sclerotic thickenings of the mural endocardium seen most often on the left ventricular septum below an insufficient aortic valve They are believed to be due to tension of the regurgitant stream Their openings are directed toward the aortic valve Similar pockets directed toward the apex, are found in the left atrium just above the mitral valve

Among other regressive lesions are occasional instances of *mucoid* or *amyloid degeneration*

Not uncommonly in the hearts of newborn or young infants, occasionally in those of children and rarely in the hearts of adults, are found single or multiple *endocardial blood cysts* or *tumors* These are pink or dark red circumscribed nodules, chiefly on the leaflets of the mitral or tricuspid valves and composed of endothelial lined lacunae of blood They have been interpreted as hemangiomata or as hematomata

Mural Thrombosis Mural endocardial thrombi involving chiefly the left ventricle occur in cases of myocardial infarction With extensive septal infarction mural thrombi may also develop in the right ventricle Right and left ventricular mural thrombi have been described in certain cases of cardiac hypertrophy of obscure origin In cases of advanced congestive heart failure, especially with atrial

fibrillation, mural thrombi may occur in any chamber but predominantly in the atria and the atrial appendages. An underlying rheumatic atrial endocardial lesion may favor the development of mural thrombi. The thrombi may be of clinical importance because they are sometimes the source of systemic or pulmonary emboli.

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Chapter 26

MITRAL VALVULAR DISEASE

Valvular heart disease is a major cardiac ailment which corresponds in incidence with its chief cause rheumatic fever Mitral valvular disease is most common aortic stenosis or insufficiency next while tricuspid disease occurs occasionally and pulmonic valvular disease rarely Combined mitral and aortic disease is common in the rheumatic cases, in about 10 per cent the tricuspid valve is also affected The frequency of aortic insufficiency is increased in regions where syphilis is common

Valvular heart disease is presented as a separate subject because it is often encountered when there are neither symptoms nor a history of the causative disease Certain clinical features of valvular disease are identical and may be described in common whatever the cause Finally, the disturbances in circulatory dynamics the symptomatology and the type of heart failure are determined more often by the valvular lesion than by the disease which produced it This is not to obscure the fact, however that the presence of active rheumatic inflammation, the severity and extent of myocardial damage the association of hypertension and the interference with coronary blood flow by atherosclerosis or syphilitic ostial stenosis are vital factors which reduce the ability of the heart to tolerate the strain of valvular disease, and which may lead to heart failure

ETIOLOGY OF MITRAL VALVULAR DISEASE

Rheumatic endocarditis is responsible for the great majority of cases of mitral valvular disease It may produce mitral stenosis or mitral insufficiency, but usually mitral stenosis is combined with some degree of insufficiency However as a rule the physical signs and the cardiac disturbances are determined by the predominant mitral insufficiency or by predominant mitral stenosis

Occasionally there is pure organic *mitral insufficiency* Brigden and Leatham[41] studied a series of 30 cases of mitral insufficiency, which they thought might not be rheumatic because in contrast with mitral stenosis which affects females predominantly, these occurred chiefly among males Furthermore there was rarely a history of rheumatic fever

Other rare causes of organic mitral insufficiency are bacterial endocarditis, traumatic rupture of a cusp or of the chordae tendineae spontaneous rupture of the chordae and rupture of a papillary muscle secondary to bacterial endocarditis or coronary occlusion The occasional occurrence of severe mitral insufficiency in children below the age of 5 and without a history of rheumatic fever suggests that there are rare instances of congenital mitral insufficiency Congenital mitral insufficiency may be due to perforations in the valve leaflets or to a congenital cleft in the septal leaflet of the mitral valve Traumatic mitral insufficiency is now due in most instances to injury of the valve in the course of mitral valve surgery

Relative or functional mitral insufficiency occurs commonly as a result of pronounced dilatation of the left ventricle due to hypertensive, coronary or aortic valvular disease, usually in association with left ventricular failure Imperfect valvular closure under such circumstances is due to dilatation of the mitral ring and to retraction of the cusps by chordae and papillary muscles as the ventricular chamber elongates

Mitral stenosis is almost always due to rheumatic endocarditis Occasionally it is a congential lesion[87] due either to anomalous development or to fetal endocarditis e g in the cases of Lutembacher s syndrome (p 735) Functional mitral stenosis may result from obstruction of the valvular orifice by bacterial vegetations atrial thrombi or tumors Congenital mitral atresia has been reported (p 791)

Rheumatic mitral valvular disease occurs two or three times as frequently among females as among males

PATHOLOGY OF MITRAL VALVULAR DISEASE

Rheumatic Mitral Disease

The rheumatic valvulitis and verrucae lead to scarring thickening shortening and deformity of the cusps and retraction of their free margins[■ 134] At the same time similar inflammatory changes and fibrosis cause thickening fusion and shortening of the chordae tendineae

Mitral Insufficiency characterized by incomplete closure of the mitral orifice with consequent systolic regurgitation of blood into the left atrium results from the following

1 Imperfect coaptation of the valve cusps because of their rigidity deformity and retraction Retraction and contraction of the scarred cusps may so reduce their cross sectional area as to produce a significant loss of substance The regurgitation is virtually always at the posterior (posteromedial) commissure the mural or posterior leaflet being drawn down into the left ventricle or becoming adherent to the mural endocardium in its posterolateral corner

2 *Fusion and shortening of the chordae* which fix the cusps and restrain their apposition to each other thus preventing closure of the valvular orifice in systole

The contracted shortened chordae affect particularly the posterior leaflet which is held down in the ventricle and prevented from effecting valvular closure during ventricular systole

3 Inflammation and scarring of the mitral ring which dilate the orifice and interfere with the muscular systolic reduction in its circumference an important factor in its normal closure The orifice of the valve may become so large that the cusps are incapable of closing it Dilatation of the ring may be intensified by enlargement of the left ventricle due to associated aortic valvular disease or hypertension especially when complicated by left ventricular failure The enlargement of the left ventricle which results from mitral insufficiency further increases the degree of regurgitation by dilating the ring

Serious mitral insufficiency may be associated with some degree of stenosis in as many as 75 per cent of the cases but the stenosis is rarely significant Conversely some degree of insufficiency accompanies most cases of mitral stenosis but the degree of insufficiency becomes insignificant when the stenosis is very severe In a number of cases there is a high degree of stenosis due to fusion and calcification of the leaflets at the anterior commissure while shortening loss of substance or adhesion at the posterior commissure causes significant regurgitation in that region

Mitral stenosis results from repeated rheumatic inflammation and healing It is probable that at least two years are required for the development of mitral stenosis after the initial attack of rheumatic valvulitis Mitral stenosis results from the following valvular abnormalities

1 Fusion of adjacent leaflets at their commissures to form a single circular curtain The mitral opening may be further narrowed by continued contraction of the scar tissue and by subsequent calcification of the mitral ring and cusps

2 Rigidity of the valve cusps due to fibrosis *This keeps them fixed in a position* which narrows the mitral orifice

3 Fusion and shortening of the chordae tendineae and their absorption into the mitral *cusps resulting in a funnel shaped structure* which accentuates the narrowing of the orifice In other instances adhesion and shortening of the cusps produces a diaphragmatic slit *described as the button hole or fish* mouth type of mitral stenosis

As a result of these changes two major types of mitral stenosis have been described[131 14] In about 80 to 90 per cent of operated cases the leaflets have undergone fibrous contraction are rigid and form a stenotic opening with little thickening or fusion of the chordae tendineae In this type calcification is very common In the second relatively infrequent type the scarred leaflets form an elastic funnel and in addition the chordae tendineae are shortened fused and often firmly adherent across the valvular opening[4] Whereas the results of surgery are usually good in the first type they are relatively poor in the second In the latter the elastic valve does not yield readily to finger fracture and even when the fused cusps are incised the fused interlacing chordae tend to maintain the stenosis of the mitral orifice

The normal area of the fixed orifice of the

mitral valve is 5 sq cm Narrowing to between 1 and 2 sq cm is associated with only mild mitral stenosis from the clinical view point since normal blood flows may be attained with moderate elevations in left atrial pressure In moderate to severe cases of mitral stenosis the mitral orifice has an area of less than 1 sq cm and even less than 0 5 sq cm The term "tight" mitral stenosis is applied to those cases in which the mitral orifice admits only a probe

Atherosclerotic (Calcific) Mitral Disease

Isolated white collagenous plaques of thickening and yellow atheromatous patches are almost always found in normal valves even in those of children More extensive degenerative changes occur with increasing age especially on the ventricular surface of the anterior (aortic) mitral cusp These lesions are of no clinical significance

Calcification of the annulus fibrosus or ring of the mitral valve has been found in 10 per cent of hearts at necropsy, with greatest frequency among the aged and among women [85] This lesion is clinically unimportant but may cause a loud rough or musical apical systolic murmur and may be discovered by careful fluoroscopic examination [9] Usually calcification of the mitral ring is of degenerative origin [III 193] and is not accompanied by calcification of the cusps On the other hand, calcification of the valve cusps is almost always secondary to rheumatic inflammation and occurs commonly in advanced mitral stenosis and/or insufficiency Calcification of inflammatory origin may also involve the mitral ring Calcification of the mitral ring or cusps may be associated with calcific aortic stenosis and occasionally with calcific deposits in the fibrous septum The latter may damage the bundle of His and produce complete heart block or other disturbances in conduction [40] The frequency of congestive heart failure angina pectoris or conduction disturbances in cases of calcification of the mitral ring or cusps is due to associated rheumatic cardio valvular disease or to coronary atherosclerosis and not to the direct effects of the calcium deposits

Rarer Forms of Mitral Disease

Bacterial endocarditis (Chapter 34) may produce mitral insufficiency by perforation of a cusp, by formation of a valvular aneurysm or by rupture of chordae tendineae or a papillary muscle The severity of clinical mitral insufficiency due to rupture of chordae tendineae or of a papillary muscle attests to the importance of these structures in the closure of the mitral orifice Functional mitral stenosis rarely results from obstruction of the orifice by cauliflower like vegetations I have seen an infected ball thrombus in the left atrium cause intermittent complete obstruction with shock and peripheral gangrene [208] Syphilis (Chapter 35) rarely involves the mitral valve either as a gumma or by contiguous extension from a luetic aortitis [14] The syphilitic myocarditis may simultaneously involve the bundle of His and produce heart block Mitral stenosis due to tumors is discussed in Chapter 45

Rupture of the mitral valve[19] may cause mitral insufficiency by perforation or tear of a cusp or by rupture of chordae or a papillary muscle Spontaneous rupture of chordae tendineae usually of previously diseased valves has also been noted [14]

The Heart in Mitral Valvular Disease

The *left atrium* is considerably dilated and hypertrophied in both mitral insufficiency and stenosis Sometimes it enlarges to giant proportions (aneurysmal dilatation of the left atrium), rarely attaining a volume of 2 or 3 liters [191] This is usually associated with severe mitral insufficiency occasionally with mitral stenosis Rarely a giant left atrium erodes the spine at the level between D5 and D9 [7] The variable degree of left atrial enlargement independent of the degree of mitral stenosis or insufficiency appears to be related to intrinsic differences in the atrial muscle, but the exact factors responsible are unknown

The *left ventricle* is dilated and hypertrophied in cases of predominant mitral insufficiency, or when prolonged mitral insufficiency precedes stenosis In hearts with predominant mitral stenosis the left ventricle may be of normal size But with pronounced and longstanding mitral stenosis the left ventricle may become smaller than normal and even atrophic The decreased size of the chamber is particularly confined to the posterior half or the so called inflow tract [152] An associated aortic valvular disease may produce enlargement of the left ventricle

The *right ventricle* usually enlarges and becomes hypertrophied, especially after the development of pulmonary hypertension due to

left atrial failure The *right atrium* also becomes dilated with progressive right heart failure

The Lungs in Mitral Valvular Disease

As a result of prolonged congestion and fibrosis the lungs become reddish brown firm dense and dry (brown induration of Virchow)[111] Infarcts due to pulmonary embolism hemorrhagic areas due to rupture of small vessels and atherosclerosis of the pulmonary arteries are also observed on gross examination The hemorrhages may give rise to nodular accumulations of granular hemosiderin chiefly within the alveoli[180, 95, 278]

The microscopic changes have been described by zu Jeddeloh[144] and by Parker and Weiss[191] and others[137, 180, 110, 95, 77, 278] The alveolar walls are markedly thickened by interstitial edema increased collagen and widening of the capillary basement membrane The width of the alveolar wall may increase from a normal of 1 to 3 micra to 30 to 50 micra Heart failure cells which arise from alveolar epithelium or reticuloendothelial cells and which contain brownish iron pigment derived from hemorrhage are observed in the alveolar lumina These cells are often extruded into the sputum The capillaries become congested wider than normal elongated and beaded and project into the alveolar lumina and the arterioles or small arteries undergo thickening of their wall and narrowing of their lumina[131, 106] These various changes interfere with pulmonary ventilation by making the lung rigid and inelastic and with diffusion and oxygenation of the blood by widening the alveolar-capillary wall The increased resistance in the congested capillaries and the narrowed pulmonary arterioles or small arteries impose a strain on the right ventricle

MITRAL INSUFFICIENCY

PATHOLOGIC PHYSIOLOGY

Magnitude and Dynamics of the Leak[110]

The magnitude of the regurgitant stream is determined by the area of the mitral orifice which is not closed during ventricular systole and by the pressure relations in the left ventricle left atrium and the aorta A serious degree of insufficiency may be represented by regurgitation of 10 to 30 cc per beat while leaks of 30 to 100 cc or more may be encountered in the most severe cases of mitral insufficiency Leaks of less than 10 cc per stroke are regarded as small and those below 5 cc as virtually insignificant

The pressure gradient between the left ventricle and the left atrium during systole is much higher than that between the left ventricle and the aorta Therefore there is a large reflux into the left atrium during ventricular systole even if the mitral opening is much smaller than that into the aorta Even moderate incompleteness of closure of the valve orifice may cause a sharp reduction in cardiac output which is the major physiologic defect in mitral insufficiency[107, 106] It has been estimated that regurgitation through an extent of one fifth of the cross-sectional area of the mitral orifice may reduce the cardiac output 50 per cent

Compensation of the Left Atrium

Experimental studies[226, 176] indicate that the normal ventricular output can be restored despite regurgitation into the left atrium of 50 per cent of the total stroke volume The volume of blood in the left atrium during its diastole is greater than normal because of the regurgitant stream it receives from the left ventricle in addition to the usual inflow from the pulmonary veins This results in increased left atrial pressure and increased stretch of the atrial musculature The increased atrial pressure promotes the left atrial output during atrial diastasis The increased stretch results in a stronger atrial contraction according to Starling's law of the heart Thus the left atrium compensates for the mitral insufficiency by a greater output But the greater diastolic volume and pressure in the left atrium lead to dilatation and hypertrophy of that chamber

The augmented blood flow from the left atrium into the left ventricle is favored by bradycardia with prolongation of diastole Conversely compensation for mitral insufficiency may be seriously impaired by tachycardia and shortening of the diastolic period

Compensation of the Left Ventricle

The enlarged output of the left atrium increases the diastolic volume and pressure of the left ventricle This leads to a more forceful contraction and an augmented ventricular discharge of blood In this manner the normal effective output into the aorta is restored but the actual output is equal to the output into the aorta plus the regurgitant outflow into the

left atrium An essential feature in left ventricular compensation is the speedy elevation of pressure during its isometric contraction, before there is any ejection or regurgitation of blood[44] The increased diastolic volume and pressure in the left ventricle lead to dilatation and hypertrophy of this chamber Thus compensation of mitral insufficiency is effected by dilatation and hypertrophy of both the left atrium and ventricle, but only at the expense of increased work for these chambers Furthermore as the left ventricle enlarges it leads to or enhances dilatation of the mitral ring thereby increasing the degree of mitral regurgitation Eventually the hypertrophied left ventricle may maintain an adequate output only at rest, but not with exercise When the left ventricle fails its output is inadequate and the left ventricular diastolic pressure rises

The Lungs and Right Heart

In pure rheumatic mitral insufficiency compensation may be effective if the magnitude of the leak is small or moderate and the left atrial and ventricular musculature is not seriously damaged But with large leaks left atrial compensation is rarely effective and there is some degree of pulmonary congestion Pulmonary hypertension gradually develops and the right ventricle becomes hypertrophied Eventually the right ventricle fails and right ventricular diastolic and right atrial pressure rise When mitral insufficiency appears suddenly as a result of trauma or spontaneous rupture of the chordae tendineae there is a rapid development of pulmonary congestion hypertension of the pulmonary circulation and right ventricular enlargement associated with heart failure

CLINICAL FEATURES OF MITRAL INSUFFICIENCY

Clinical Varieties

Clinical manifestations and course vary considerably according to the severity of the lesion Some patients are virtually asymptomatic and, except for the presence of an apical systolic murmur and perhaps some evidence of left ventricular hypertrophy, present no important manifestations of cardiac disease In a second group of patients there is more definite evidence of left atrial and left ventricular enlargement and there may be annoying palpitation due to multiple ventricular or atrial premature beats and dyspnea on more than moderate exertion There are many cases of pure organic mitral insufficiency in which the course is relatively long and benign but in which heart failure, when it develops, is severe and rapidly progressive[98] The importance of the cases with relatively benign and asymptomatic mitral insufficiency is that bacterial endocarditis may complicate and shorten their course Finally, there are the cases with large leaks, disabling symptoms and unfavorable course and which are often difficult to distinguish from mitral stenosis These are the cases which are to be considered for surgical correction as soon as a satisfactory operation becomes fairly standardized and generally acceptable

Symptoms and Signs

Palpitation and dyspnea are the earliest symptoms of mitral regurgitation But in the more severe cases dyspnea on slight exertion or even at rest orthopnea and fatigability are outstanding symptoms Gorlin et al[107] stressed that fatigue or weakness is more prominent than dyspnea in mitral regurgitation in contrast with mitral stenosis But this finding varies in different patients and with the stage of the disease, and cannot be used in differentiating the two conditions In some patients analysis of the fatigability indicates that it is definitely due to dyspnea and fatigue of respiratory muscles, but in others the fatigue is related to the legs, suggesting that it is due to inadequate cardiac output at rest or with exertion Right ventricular failure is relatively infrequent until late in the course but when it develops it is usually progressive and intractable Hepatic enlargement and tenderness marked venous engorgement peripheral edema and ascites are common In several patients the development of right heart failure was associated with atrial flutter or flutter fibrillation Not only was this difficult or impossible to convert to normal sinus rhythm with quinidine, but the rapid ventricular rate could not even be slowed adequately by either quinidine or large doses of digitalis Atrial thrombosis and peripheral emboli are much less common than in cases of pure mitral stenosis

Cardiac Findings

The outstanding finding is the presence of an apical systolic murmur, which is loud and prolonged, often replaces the first heart sound or starts immediately after it, and occupies most of systole (holosystolic) Occasionally is occurs late in systole It may be decrescendo

i e diminishing in intensity from the beginning to the end of systole or crescendo [41] High pitched musical murmurs are common in mitral insufficiency The murmur is usually loudest at or near the apex and radiates to the axilla and not infrequently toward the base of the heart and to the back in the left subscapular region Unlike the systolic murmur of tricuspid insufficiency it becomes softer on inspiration A systolic thrill accompanies the very loud murmurs especially in cases of mitral regurgitation due to ruptured chordae tendineae or papillary muscle There may be no systolic murmur in proven cases of significant mitral regurgitation when accompanied by mitral stenosis but this is exceptional [184 114] Elkin and associates[72] reported the absence of a systolic murmur in 5 patients submitted to operation for mitral stenosis but found to have a significant mitral regurgitant jet at operation

The second pulmonic sound is usually accentuated and may be split The second sound at the apex may be faint or inaudible being included in the systolic murmur A third heart sound occurs frequently but no opening snap [41] The apex beat may be displaced downward and outward and may be palpable as a heaving thrust in the sixth interspace lateral to the midclavicular line In cases of giant left atrium extending beyond the right border of the heart there may be a systolic propulsion of the right chest [99] Evidence of enlargement of the left atrium and ventricle often requires roentgen ray examination

Roentgenologic Examination of the Heart in Mitral Insufficiency

In the anteroposterior view the lower left cardiac border representing the left ventricle extends abnormally outward and downward and may be unusually rounded Posterior enlargement of the left ventricle is best seen in the left anterior oblique view There may be a slight prominence due to a large left atrium or atrial appendage where the left ventricle approaches the junction to the pulmonary artery The barium-containing esophagus is displaced to the right in anteroposterior views and posteriorly in the right oblique view by the curve of the enlarged left atrium When failure supervenes the pulmonary markings are increased because of vascular congestion and the right cardiac contour is greatly widened because of right atrial and ventricular dilatation

Fluoroscopic examination often discloses systolic expansion of the left atrium [7 1] but this may be absent with small leaks marked enlargement of the left atrium tachycardia or an atrial arrhythmia or when the atrial border cannot be distinctly visualized Pulsation of the left atrium in mitral regurgitation has also been observed by roentgenkymography or electrokymography [63 111 178] and is recorded as an early rise in systole with a flat top (plateau) A similar systolic plateau occurring late in systole is said to suggest mitral stenosis [189]

If the left atrium is of unusual proportions its shadow may appear along the right border Then the right lower arch is due to the right atrium and the right middle arch to the overlapping left atrium These two arches may show pulsations in opposite directions giving a see-saw effect The upper pulsation (left atrium) expands laterally in systole owing to the regurgitation of blood from the left ventricle the lower (right atrium) moves medially in systole due to the transmitted pulsation of the right ventricle

Electrocardiogram in Mitral Insufficiency

In contrast with the electrocardiogram of mitral stenosis that of insufficiency shows a tendency to left axis deviation In the majority of cases of significant mitral regurgitation there is evidence suggesting left ventricular hypertrophy best seen in precordial leads The P waves may be tall but are more likely to be normal than in mitral stenosis [41]

Ballistocardiogram

A consistent abnormal headward wave was found preceding the J wave [184] But Izak and Braun[184a] could not confirm its specificity

Pulmonary capillary and left atrial pressure curves[134 136 15 151 193] usually show an a wave of atrial contraction and a gradually rising V wave in systole In mitral insufficiency there is often a single large positive wave (plateau) throughout systole due to regurgitation of blood from the left ventricle

DIAGNOSIS

The diagnosis of mitral insufficiency is based primarily on the presence of a loud prolonged apical systolic murmur and enlargement of the left atrium and ventricle A history of rheumatic fever is supporting evidence Demonstration of systolic expansion of the left atrium is also diagnostically important but not conclusive Pulse tracings of

the pulmonary capillary[7,8] (by a catheter wedged into a small pulmonary artery) or of the left atrium by needle puncture through the chest wall[150] or bronchoscope[3] or by a balloon in the esophagus,[158] may disclose a systolic plateau due to the regurgitant jet, but this is not reliable in individual cases[249]. For differential diagnosis from mitral stenosis, see page 666

The *diagnosis of mitral insufficiency due to non rheumatic causes* is based on the sudden development of a loud apical systolic murmur in the course of bacterial endocarditis or myocardial infarction after penetrating or non penetrating chest injury or after an unusual, severe exertion Spontaneous rupture of mitral chordae is suggested by the development in a middle aged or elderly person without striking cause of a loud apical murmur and thrill followed in a few days weeks or months by enlargement of the left atrium and ventricle and by congestive heart failure Rupture of a papillary muscle is more likely to be followed by rapid heart failure, shock, acute pulmonary edema and death Rupture of a congenital aneurysm of the sinus of Valsalva must also be differentiated (p 773) Aortic stenosis may be associated with a systolic murmur which is loudest at the mitral area

Relative or functional mitral insufficiency is suggested by the presence of an apical systolic murmur in a patient with hypertension or coronary heart disease and heart failure If the mitral murmur disappears with improvement of the circulatory status, the functional nature of the disturbance is confirmed

Calcification of the mitral ring may be disclosed by a harsh or musical apical systolic murmur and by fluoroscopic visualization of a U or J shaped calcification in the region of the annulus fibrosus (Fig 118)

Calcification of the mitral leaflets can be dif



Fig. 118 Calcification of mitral ring J shaped density (arrow) Fluoroscopy and kymography revealed wide pulsations toward apex Al a calcification of pericardium

ferentiated from calcification of the ring and almost always denotes organic rheumatic mitral insufficiency or stenosis[2,9] Calcification in the cusps appears fluoroscopically as groups of irregular nodular masses in the posterior third of the heart moving downward toward the apex with ventricular systole[13]

The Functional Systolic Murmur

The greatest problem in the differential diagnosis of mitral insufficiency is to distinguish an organic mitral murmur from a so called *functional* one[1,4] A non significant physiologic or functional systolic murmur has been described in 30 to 90 per cent of children or adolescents[9,131,172] Often the murmur may be heard after exercise when it is absent during rest[214] The incidence of functional systolic murmurs diminishes rapidly in adult life That systolic murmurs often appear with anemia fever and hyperthyroidism suggests that they result in these conditions from the increased velocity of blood flow Many functional murmurs are of cardiorespiratory origin arising as a result of compression of the overlying lobule of lung when the heart contracts Chisholm[50] suggested that functional pulmonic systolic murmurs may occasionally be due to unequal stretching of the pulmonary artery with change of position forced inspiration or as a result of pleural adhesions Under these circumstances the valve cusps are apposed in such a way (trigonoidation of the semilunar cusps) as to act as an obstruction to the outflow of blood

Although there is no certain method of differentiating organic from functional murmurs the following points are helpful Functional murmurs are often loudest in the pulmonic area radiate little and are faint in intensity A close relation between the intensity of a systolic murmur and the presence of organic heart disease has been indicated by the studies of Freeman and Levine[84] Baker et al[17] Boone and Levine[25] and of Kuttner and Markowitz[156] Functional murmurs usually disappear when the breath is held in inspiration These differences permit a statistical differentiation of organic from functional murmurs when dealing with large numbers of persons but are not decisive in the individual case

The association of cardiac enlargement with an apical systolic murmur usually denotes that the murmur is organic (in the absence of left ventricular failure) But organic mitral insufficiency may be characterized by an apical systolic murmur without demonstrable cardiac enlargement Thus Boone and Levine[25] observed 225 individuals with a history of rheumatic fever with faint or distinct systolic murmurs but without cardiac enlargement During an average observation period of 9 6 years 42 per cent of those with a distinct systolic murmur developed mitral stenosis aortic insufficiency or both in contrast with 4 8 per cent of those with soft poorly transmitted murmurs Similarly Kuttner and Markowitz[156] after an eight year follow up period observed the development of definite organic heart disease in 48 per cent of 144 rheumatic children with a loud blowing apical systolic murmur but without cardiac enlargement and in 13 per cent of 171 cases of potential or possible heart disease in which the murmur was soft and poorly transmitted For practical purposes it is important to view all systolic murmurs with suspicion and to attempt to determine their cause This viewpoint often leads to the discovery of rheumatic mitral valvular disease or calcific aortic stenosis sickle cell or other anemia hyperthyroidism or hypertension Not infrequently especially in older individuals the finding of an apparently insignificant systolic murmur suggests the possibility of subacute bacterial endocarditis when the diagnosis otherwise appears obscure In young persons without a history of rheumatic fever and without cardiac enlargement or other evidences of cardiovascular disease care must be taken not to make a diagnosis of organic heart disease lest cardiac invalidism or cardiac neurosis be initiated even though a certain percentage of such individuals will eventually disclose unmistakable valvular heart disease Under the circumstances mentioned restriction of activity [redacted] rarely indicated On the other hand the realization that many individuals with apparently non significant systolic murmurs have organic valvular disease poses a different problem when deciding whether to accept such applicants for life insurance or military service

SURGICAL TREATMENT OF MITRAL INSUFFICIENCY

A variety of surgical techniques have been used to correct mitral insufficiency[10,12,58,147,161] but there is currently no uniform procedure which has gained general acceptance The

the pulmonary capillary [78, 3] (by a catheter wedged into a small pulmonary artery) or of the left atrium by needle puncture through the chest wall [56, 8, a] or bronchoscope[3] or by a balloon in the esophagus [68] may disclose a systolic plateau due to the regurgitant jet but this is not reliable in individual cases [249, 1] For differential diagnosis from mitral stenosis see page 666

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The greatest problem in the differential diagnosis of mitral insufficiency is to distinguish an organic mitral murmur from a so-called functional one [3,4] A non significant physiologic or functional systolic murmur has been described in 30 to 90 per cent of children or adolescents [9,181,172] Often the murmur may be heard after exercise when it is absent during rest [214] The incidence of functional systolic murmurs diminishes rapidly in adult life That systolic murmurs often appear with anemia fever and hyperthyroidism suggests that they result in these conditions from the increased velocity of blood flow Many functional murmurs are of cardiorespiratory origin arising as a result of compression of the overlying lobule of lung when the heart contracts Chisholm[10] suggested that functional pulmonic systolic murmurs may occasionally be due to unequal stretching of the pulmonary artery with change of position forced inspiration or as a result of pleural adhesions Under these circumstances the valve cusps are apposed in such a way (trigonoidation of the semilunar cusps) as to act as an obstruction to the outflow of blood

Although there is no certain method of differentiating organic from functional murmurs the following points are helpful Functional murmurs are often loudest in the pulmonic area radiate little and are faint in intensity A close relation between the intensity of a systolic murmur and the presence of organic heart disease has been indicated by the studies of Freeman and Levine[94] Baker et al [17] Boone and Levine[38] and of Kuttner and Markowitz [153] Functional murmurs usually disappear when the breath is held in inspiration These differences permit a statistical differentiation of organic from functional murmurs when dealing with large numbers of persons but are not decisive in the individual case

The association of cardiac enlargement with an apical systolic murmur usually denotes that the murmur is organic (in the absence of left ventricular failure) But organic mitral insufficiency may be characterized by an apical systolic murmur without demonstrable cardiac enlargement Thus Boone and Levine[38] observed 225 individuals with a history of rheumatic fever with faint or distinct systolic murmurs but without cardiac enlargement During an average observation period of 9 6 years 42 per cent of those with a distinct systolic murmur developed mitral stenosis aortic insufficiency or both in contrast with 4 8 per cent of those with soft poorly transmitted murmurs Similarly Kuttner and Markowitz [153] after an eight year follow up period observed the development of definite organic heart disease in 48 per cent of 144 rheumatic children with a loud blowing apical systolic murmur but without cardiac enlargement and in 13 per cent of 171 cases of potential or possible heart disease in which the murmur was soft and poorly transmitted For practical purposes it is important to view all systolic murmurs with suspicion and to attempt to determine their cause This view point often leads to the discovery of rheumatic mitral valvular disease or calcific aortic stenosis sickle cell or other anemia hyperthyroidism or hypertension Not infrequently especially in older individuals the finding of an apparently insignificant systolic murmur suggests the possibility of subacute bacterial endocarditis when the diagnosis otherwise appears obscure In young persons without a history of rheumatic fever and without cardiac enlargement or other evidences of cardiovascular disease care must be taken not to make a diagnosis of organic heart disease lest cardiac invalidism or cardiac neurosis be initiated even though a certain percentage of such individuals will eventually disclose unmistakable valvular heart disease Under the circumstances mentioned restriction of activity is rarely indicated On the other hand the realization that many individuals with apparently non significant systolic murmurs have organic valvular disease poses a different problem when deciding whether to accept such applicants for life insurance or military service

SURGICAL TREATMENT OF MITRAL INSUFFICIENCY

A variety of surgical techniques have been used to correct mitral insufficiency [19,3, 49,147,101] but there is currently no uniform procedure which has gained general acceptance The

procedure employed differs with the pathologic disturbance responsible for the regurgitation[89] In the cases of predominant mitral stenosis with rigid, fused cusps and a small regurgitant jet separation of the fused cusps with restoration of their mobility usually corrects not only the stenosis but also the regurgitation

The more severe forms of mitral insufficiency are usually of two types (1) There is a loss of valve substance, preventing the normal overlapping or even the coaptation of the cusps to close the mitral orifice As a rule it is the posterior (mural) leaflet which is responsible and the regurgitant leak is at the posteromedial commissure (tear drop opening) or occasionally in the center of the orifice (crescent-shaped opening between the cusps) The rigid narrowed cusps form a flat diaphragm with a crescentic or buttonhole opening In these cases division of the commissures usually increases the regurgitation Surgical procedures attempt to correct this type of insufficiency by suturing together the lips of the valve at its incompetent portion or by the insertion of a graft or prosthesis to substitute for or reinforce the defective portion of the cusps

(2) A common cause of large regurgitant leaks is an enlarged stretched or malfunctioning mitral annulus which is too large to be occluded Consequently the cusps, even when freely mobile do not approximate in ventricular systole In fact the cusps may become more widely separated and the regurgitation increased during systole Attempts have been made to reduce the circumference of the annulus (and therefore the cross section of the mitral orifice) by suturing the annulus or by inserting grafts or prostheses

Occasionally mitral insufficiency is due in large measure to adherence of the cusps to shortened chordae tendineae which keep the cusps, especially the mural cusp fixed in the ventricular cavity and prevent closure of the mitral orifice In such cases the finger passed through the atrial appendage and mitral orifice (p 673) draws the affected cusp upward to free it of its adhesions If this is impossible the cusp is mobilized by severing the shortened chordae and scar tissue by a flexible or right angle neurectomy knife introduced through the left ventricular wall while the finger in the mitral valve guides it[147]

Detailed description of the operative procedures is unwarranted until one of those presently available, or some other technique is generally accepted as most satisfactory In general any significant mitral stenosis is corrected first and an effort is then made to free the posterior (mural) leaflet from any adhesions to the shortened chordae or mural endocardium and elevate it to its proper position Bailey et al[12] employed pericardial grafts in a series of 150 patients operated on for mitral insufficiency, and a similar procedure was used by Logan and Turner[168] The creation of a transventricular "hammock" by means of a pedicled pericardial graft was associated with improper placement and occlusion of the orifice, hemolysis of blood eventual atrophy of the graft and a high mortality[184] Harken and associates used various synthetic prostheses in operations on 51 patients with mitral insufficiency most recently a lucite spindle baffle which substitutes for the loss of valve tissue[10] The teardrop shaped spindle is anchored at one end beneath the leaflets and annulus in the left ventricle, and the larger end is fixed above the annulus posteriorly There has been general objection to the use of foreign substances in the heart because of the danger of their becoming free and the relatively high mortality rate associated with the operation

Davila and associates[69] employed a constricting (circumferential) suture to decrease the size of the atrioventricular annulus and recently reported satisfactory results in 12 clinical cases of mitral insufficiency[101] By means of suturing Hurwitt et al[134] corrected experimental mitral insufficiency by plicating the annulus from the epicardial surface of the left ventricle without compromising the coronary circulation Kay and Cross[147] noted that anterior displacement of the posterior wall of the atrium at the level of the mitral orifice obliterated the regurgitant jet Accordingly they devised a technique to reduce the size of the mitral ring at the posteromedial commissure Nichols has devised a technique whereby limited apposed portions of the mitral valve ring over either or both valve poles, are approximated by mattress suture[191] In 17 patients thus operated on there was a striking immediate reduction in the size of the digitally palpable regurgitant stream There were 3 postoperative deaths In all but one case there was auscultatory improvement and striking clinical benefit

MITRAL STENOSIS

PATHOLOGIC PHYSIOLOGY

Alterations in Hemodynamics[48, 88, 142, 111]

Size of the Mitral Orifice In animal experiments[3] significant circulatory disturbances occur only when the mitral orifice is narrowed to less than one quarter of its normal size In man the normal area of the mitral orifice ranges between 4 and 6 sq cm Serious circulatory disturbances and consequent clinical symptoms arise only when this area is reduced to less than 1 sq cm In symptomatic mitral stenosis the mitral orifice usually measures between 0 5 and 1 1 sq cm[142]

Left Atrial and Pulmonary Capillary Pressures[104, 104a, 104] The resistance afforded by a narrowed mitral orifice results in an increased left atrial pressure Since there are no valves between the atrium and the pulmonary veins the rise in left atrial pressure is reflected by that in the pulmonary veins and capillary The pulmonary capillary pressure is measured preoperatively by wedging the cardiac catheter into the extreme periphery of a branch of the pulmonary artery[229] Whether this pressure actually represents pulmonary capillary pulmonary venous or even pulmonary arteriolar pressure, it is an approximation of the left atrial pressure and of the resistance offered by the narrowed mitral valve Left atrial pressures have been measured by venous catheterization[48] (when there was an associated atrial septal defect) by needle puncture through the bronchoscope[8] suprasternal notch[20a] or chest wall[30, 247] or by direct puncture during cardiac operations[5] The greater the blood flow the higher the left atrial and pulmonary capillary pressure for a given degree of mitral stenosis i e for a given mitral resistance Therefore the left atrial and pulmonary capillary pressures rise with the increased flows usually associated with exercise

The normal mitral orifice permits not only normal flows at rest but greatly increased flows with exercise without a rise in left atrial pressure When the mitral orifice is moderately reduced in area to about 1 5 sq cm there may be only a slight increase in left atrial pressure at rest but a marked rise with exercise In moderately severe cases of mitral stenosis with an orificial area of about 1 sq cm the mean pressure in the left atrium and pulmonary capillaries may be 15 to 25 mm Hg at rest (normal below 10 mm Hg) but with exercise this may increase to levels of 35 mm Hg or more at which pulmonary edema is likely to occur When there is more extreme mitral stenosis with a mitral orificial area of 0 5 sq cm or less such elevations of left atrial and pulmonary capillary pressures may be attained with very slight exertion since the mean *resting* left atrial pressure ranges up to 35 mm Hg and that in the pulmonary capillaries may likewise be elevated up to 35 mm Hg

The Mitral Atrioventricular Gradient Maintenance of blood flow through the narrowed mitral orifice is determined by the excess of left atrial over left ventricular pressure in diastole This diastolic atrioventricular pressure difference is termed the mitral gradient Normally there is a minimal gradient of 1 mm Hg or less Since the left ventricular diastolic pressure is usually 10 mm Hg or less and the left atrial pressure in mitral stenosis is 11 to 40 mm Hg the gradient in mitral stenosis usually varies between 5 and 30 mm Hg at rest depending on the severity of the stenosis[48, 104, 104a] Since the gradient is a direct measure of the degree of mitral stenosis successful surgical relief of the obstruction should be followed by marked reduction or virtual abolition of this gradient

Pulmonary Artery Pressure The pulmonary artery pressure for a given flow is determined by the pressure in the pulmonary capillaries and by the resistance in the pulmonary arterioles Increased blood flows up to 2 5 to 3 times the normal do not usually raise pulmonary artery pressure unless there is pulmonary vascular disease or an abnormal cardiovascular shunt Arteriosclerosis with narrowing of the pulmonary arterioles develops after prolonged increase in pulmonary capillary pressure This results in a variable increase in pulmonary arteriolar resistance which is added to the resistance represented by the high pulmonary capillary pressure The pulmonary arteriolar resistance increases from a normal of less than 50 up to 500 in moderately severe cases and up to 1500 or more dynes/second/cm^{-5} in very severe cases Pulmonary artery hypertension appears secondary to the increased pulmonary capillary and pulmonary arteriolar resistance[88] Instead of a normal pulmonary artery pressure of 30/10 with a mean of 15 mm Hg patients with severe mitral stenosis have pul

monary artery pressures of 40 to 120 systolic, 15 to 50 diastolic and 20 to 85 mm Hg mean pressure at rest.[16, 84] Furthermore, whereas the pulmonary artery pressure does not normally rise with exercise, it increases considerably in cases of mitral stenosis.

Cardiac Output (Blood Flow). Various compensatory mechanisms (infra) maintain a normal cardiac output despite the mechanical obstruction at the stenotic mitral valve. With the severer degrees of stenosis the cardiac output falls below normal at rest. In cases selected for mitral commissurotomy the cardiac index at rest is usually 1.5 to 2.5 liters per minute per square meter of body surface area, instead of the normal of 3.2. Furthermore, there is an inability to increase this output with exercise as occurs normally, or there is no increase whatever, i.e., the blood flow through the mitral orifice is maximal at rest. Occasionally, during exercise, a reduction in cardiac output is found.

Oxygen Consumption and Arteriovenous Oxygen Difference. The oxygen consumption (normally 130 cc. per minute) is usually normal or slightly elevated at rest, the latter increasing with the degree of heart failure. The rise in oxygen consumption with exercise is relatively limited compared to normal, and a large oxygen debt may be sustained. Of significance is the fact that the increased oxygen consumed during exercise is delivered to the tissues not by an increase in blood flow as is the major factor normally, but by increased extraction from the blood as indicated by an increased arteriovenous oxygen difference. Even at rest, the patient with severe mitral stenosis and diminished cardiac output obtains an adequate tissue oxygen supply by an abnormally large arteriovenous oxygen difference (5 to [redacted] instead of 4.2 vol. per cent).

Compensation by the Left Atrium

Mitral stenosis tends to diminish the inflow of blood from the left atrium into the left ventricle and the left ventricular stroke output, but with moderate degrees of stenosis the normal output is restored by the following mechanisms:

1. The residual blood in the left atrium plus the normal inflow from the pulmonary veins increases the diastolic volume and diastolic pressure in that chamber.

2. The elevated pressure in the distended left atrium and the consequent diastolic atrioventricular gradient increase the ventricular inflow during early diastole.

3. In late ventricular diastole the heightened diastolic tension in the left atrium leads to a more forceful atrial contraction and [redacted] greater discharge into the left ventricle (Starling's Law of the Heart).

The effectiveness of left atrial compensation is limited because of its relatively weak musculature, by the frequent active or inactive lesions of rheumatic fever in this chamber and often by the development of atrial fibrillation. Tachycardia and the abbreviation of diastole greatly impair these compensations. With extreme narrowing of the mitral orifice (0.5 sq. cm. or less), these compensations can no longer maintain [redacted] normal cardiac output at rest, and the normal ability to increase blood flow through the mitral orifice with exercise is diminished or completely lost.

Compensations in Pulmonary Circulation and Right Ventricle

The obstruction at the mitral orifice results in a rise in pressure and increased resistance in the pulmonary veins and capillaries. The right ventricle maintains its normal output despite this increased resistance by a more forceful contraction according to Starling's Law, and consequently the pulmonary arterial pressure and right ventricular systolic pressure rise. The right ventricle becomes hypertrophied. The subsequent increase in pulmonary arteriolar resistance, due to sclerosis and narrowing of these vessels, on the one hand imposes an additional strain on the right ventricle, but on the other hand may protect the pulmonary capillaries from dangerous rises in pressure with consequent pulmonary edema. By imposing a barrier in front of the congested capillaries, the narrowed arterioles buffer the effects of a sudden increase in right ventricular output, e.g., with exercise. Eventually, the right ventricle cannot maintain a normal cardiac output against marked increases in total pulmonary resistance or can maintain it only at rest but not with exercise. The right ventricle then fails and the right ventricular diastolic as well as the right atrial and systemic venous pressures rise.

Pulmonary Function in Mitral Stenosis

The occurrence of dyspnea and associated pulmonary symptoms in mitral stenosis [redacted] re-

lated to changes in structure and function of the lungs. Certain differences in reported findings are due largely to differences in severity of the mitral stenosis, the presence or absence of heart failure, and the type and severity of the latter.

Lung Volumes (p. 971). In asymptomatic and mild cases of mitral stenosis total and timed vital capacity, maximal breathing capacity, breathing reserve, residual volume and intrapulmonary mixing were found to be normal [illegible] West et al[141] found no appreciable alterations in lung volume even with considerable pulmonary congestion if there was no pulmonary edema or hydrothorax. With increased severity of symptoms there is a progressive reduction in total and timed vital capacity and in maximal breathing capacity and a symmetrical reduction in inspiratory capacity and expiratory reserve. The symptomatic disability is disproportionate to the ventilatory effects observed and much greater than the disability in patients with pulmonary disease with similar degrees of ventilatory disturbance. The disturbances in pulmonary function are attributed to pulmonary vascular engorgement and hypertension which reduce pulmonary compliance (elasticity) and interfere with maximal air flow velocity during respiration[20,64] In severe mitral stenosis reduction in total lung capacity may be due to increasing blood volume and enlargement of the left atrium, and with heart failure to the mechanical effects of hydrothorax and ascites. Determination of the pulmonary blood volume is of uncertain accuracy. Studies with the Hamilton dye method or with Cr^{51} tagged erythrocytes[176] have shown no consistent increase in pulmonary blood volume in mitral stenosis[37, 133, 18, 141] However, an increased blood volume is present in the enlarged left atrium, and in the right ventricle when that chamber becomes enlarged.

Pulmonary Compliance and Resistance. Work of Breathing. The occurrence of dyspnea, a subjective symptom, is related to fatigue of the muscles of respiration due to the work of breathing. The force exerted by the respiratory muscles is used to overcome the elastic resistance of the lung and the resistance offered by pulmonary tissue viscance and air turbulence and viscance. Pulmonary compliance, which denotes the distensibility of the lung, is a measurement which varies inversely as the elastic resistance of the lung. Pulmonary compliance which may be measured by new techniques[119] (p. 976) is significantly reduced in mitral stenosis[119, 174] i.e., its distensibility is decreased and its elastic resistance increased. This is an early abnormality and may be present in the absence of significant ventilatory disturbance or symptoms. The reduction in pulmonary compliance is intensified during exercise[174, 5, 6] and with increasing pulmonary congestion and heart failure. All other pulmonary resistance (besides that due to elastic resistance) is increased only slightly unless there is heart failure. The work of breathing can be calculated from pressure-volume diagrams made from tracings of intraesophageal pressure and tidal volume. The work of breathing for a given alveolar ventilation is increased in mitral stenosis owing chiefly to pulmonary rigidity as measured by diminished pulmonary compliance[174] Furthermore the occurrence and degree of dyspnea and orthopnea is correlated closely with the diminished pulmonary compliance and increased work of breathing. More recent studies[1, 3] suggest that dyspnea in mitral stenosis is conditioned not by the *work* of breathing but by the *force* which has to be applied to satisfy the ventilatory demands at rest or with exercise. This force is indicated by the magnitude of the negative pleural pressure swing during inspiration.

A slight degree of hyperventilation is common in mitral stenosis[4] Normally there is an optimum respiratory rate to accomplish a given alveolar ventilation with the minimum work. In mitral stenosis this optimum frequency of respiration is significantly augmented, accounting for the rapid shallow respirations in the dyspneic patient with mitral stenosis. With exercise the oxygen consumption per liter of ventilation falls.

Alveolar Capillary Diffusion in Mitral Stenosis

The thickening of the pulmonary alveolar capillary interface commonly observed in advanced mitral stenosis appears to be associated with impaired diffusion of oxygen from the alveoli to the pulmonary capillaries[18] Carroll and Riley[49] and Fowler et al[50] found a good correlation between the impairment of diffusion and the severity of exertional dyspnea. Carroll, Cohn and Riley[48] determined that the distribution of alveolar aeration and pulmonary circulation, and the alveolar-capillary diffusion (p. 975), were normal

in 7 of 29 patients with mitral stenosis In the remaining patients they discovered either disturbances in distribution resulting in a diminished vital capacity and maximal breathing capacity or disturbances in diffusion resulting from pulmonary capillary congestion fibrosis and thickening of the alveolar capillary membrane and minimal pulmonary edema Dyspnea is not related directly to impaired alveolar capillary oxygen diffusion even though the two may be empirically correlated Increased pulmonary rigidity and increased effort of breathing which result in dyspnea, and alveolar capillary thickening with impaired diffusion both tend to appear concurrently as pulmonary consequences of severe and prolonged mitral stenosis

Arterial Oxygen Saturation and Tension[111]

The arterial oxygen saturation and tension are usually normal in mitral stenosis even in patients with dyspnea In some cases, however the oxygen saturation is reduced slightly below the normal of 95 to 98 per cent and this reduction may be intensified with exercise[4] However even slight reductions in the arterial oxygen saturation may denote more significant reductions in arterial oxygen tension, as seen in the dissociation curve of oxyhemoglobin (Fig 56 p 229) Reductions in arterial saturation in mitral stenosis particularly with heart failure are due to improper pulmonary alveolar ventilation or alveolar capillary diffusion (L factor) but sometimes also to venous admixtures (α factor)[48, 90] Finally in some patients with mitral stenosis the oxygen saturation is definitely diminished to 90 per cent or less, especially in the presence of pulmonary edema, infarction or pneumonia However, dyspnea cannot be related to diminished oxygen saturation or tension in most patients with mitral stenosis, since these are usually normal The reduction in arterial oxygen saturation is, however causally related to cyanosis when the former is definitely reduced

Blount and associates in a study of 18 subjects with mitral stenosis found the alveolar oxygen tension normal, but the arterial oxygen tension was diminished and there was consequently an increased oxygen gradient between the alveoli and arterial blood The increased gradient was interpreted as being due to an increased venous admixture (p 975) rather than to impaired diffusion

CLINICAL FEATURES OF MITRAL STENOSIS

1 Stage of Complete Compensation

Cardiac symptoms may be completely absent in patients with physical signs of mitral stenosis In these patients the mitral obstruction is of slight or moderate degree and compensation is perfect

The perfectly compensated, asymptomatic patient with mitral stenosis may live a normal life span and engage in normal physical activities But he is subject to the same complications as patients with severer mitral lesions Repeated rheumatic infections progressive contraction and adhesion of a scarred valve, or secondary calcification may intensify the obstruction and produce circulatory disturbances in a patient hitherto asymptomatic A patient with mitral stenosis may suddenly develop symptoms of pulmonary congestion or right heart failure after a prolonged period of perfect compensation Bacterial endocarditis atrial fibrillation, embolization, pulmonary infections and acute pulmonary edema may suddenly abbreviate a previously uneventful course

2 Stage of Left Atrial Failure

The majority of clinically significant cases of mitral stenosis are those in which compensation is imperfect and there are evidences of pulmonary congestion In these cases we may speak of failure of the left atrium for this chamber, although dilated and hypertrophied, is no longer able to eject or accommodate the excess of blood dammed up behind the mitral obstruction The lungs undergo alterations which interfere with the mechanics of respiration and increase the force and work of breathing (p 651) When this occurs the disease is no longer asymptomatic Some degree of decompensation is a common and early development in patients with mitral stenosis because the weak left atrium can rarely prevent pulmonary congestion for long When this congestion is slight or moderate, the patient may suffer hardly any discomfort unless he attempts some unusual physical task Thus the degree of left atrial failure and consequent pulmonary congestion is very variable and the distinction between compensation and decompensation in mitral stenosis may not be a sharp one

The following are the chief manifestations of mitral stenosis in the stage of left atrial failure but some of them may occur when the

lesion is seemingly well compensated or at any stage of the disease

Dyspnea and cyanosis are the major symptoms of mitral stenosis They result from pulmonary congestion due to failure of the left atrium A mild degree of cyanosis produces early the so-called mitral facies This is characterized by a cyanotic flush over the cheek bones and a dusky cyanosis of the lips which may be more striking following exertion Severe degrees of cyanosis are seen in long standing cases of mitral stenosis and pulmonary congestion with marked alterations in pulmonary structure

Shortness of breath is the commonest complaint in mitral stenosis and the one most disturbing to the patient Almost invariably the dyspnea is induced by exertion Rarely is it of the paroxysmal nocturnal variety encountered in the left ventricular failure of aortic hypertensive or coronary heart disease Many patients with mitral stenosis become so accustomed to a mild degree of chronic exertion dyspnea that they are hardly aware of its existence Occasionally shortness of breath is precipitated acutely perhaps by arduous exertion an infection pregnancy or the onset of atrial fibrillation Eventually dyspnea may be present even at rest At this stage *orthopnea* is generally associated

The occurrence of dyspnea and related symptoms has been correlated empirically with the height of the capillary pressure the pulmonary resistance and the pulmonary arterial pressure [35, [illegible], 35, 118, 210, [illegible]] Actually it is more directly related to the pulmonary congestion and rigidity of the lung and the consequently greater strain and work imposed on the muscles of respiration (p 654) Paroxysmal dyspnea has been particularly related to the pulmonary capillary pressure (p 649) Dyspnea on exertion or at rest is usually mild with slightly elevated mean pulmonary arterial pressures (20 to 35 mm Hg) and moderate or severe with higher mean pressures between 35 and 75 mm Hg Dyspnea may be correlated even more closely with the rise in pulmonary artery pressure on exercise Similarly mild dyspnea has been associated with moderate increases in pulmonary arterial resistance (75 to 140 dynes/second/cm^{-5}) moderate dyspnea with resistances between 150 and 500 and severe dyspnea with pulmonary arteriolar resistances between 500 and 1500 dynes/second/cm^{-5} There are however frequently examples of a disparity between the degree of dyspnea and the increase in pulmonary arteriolar resistance

Palpitation and precordial distress are early symptoms which occur almost as frequently as dyspnea They are not directly due to the pulmonary engorgement Palpitation is especially disturbing at night when the patient may be unable to fall asleep or may be awakened suddenly to become aware of forceful or rapid heart beats which occasionally skip Palpitation may be due to extracardiac factors such as indigestion excessive coffee alcohol or tobacco exertion or excitement but it appears to be induced by these causes much more readily in the heart with mitral disease than in the normal one The onset of atrial fibrillation may be heralded subjectively by palpitation and precordial distress but when the fibrillation is established and associated with a slow ventricular rate many patients are either unaware of or undisturbed by its presence

Hemoptysis has been encountered in 10 per cent of cases of mitral stenosis [347] and Thompson and Stewart[330] reported frank hemoptysis in 29 (17 per cent) of 168 cases of mitral stenosis It may occur late in the disease or it may be the initial and only subjective complaint Usually it denotes advanced mitral stenosis It may occur suddenly and be of considerable severity In 3 cases reported by Oppenheimer and Schwartz[196] and in 6 by Guizetti and Dinkler [117] the volume of a given hemorrhage amounted to between 200 and 300 cc I have seen repeated brisk hemoptysis produce a marked secondary anemia in a woman with mitral stenosis who was otherwise asymptomatic Other possible causes of hemoptysis and of secondary anemia had been thoroughly excluded In one patient with advanced mitral stenosis repeated exsanguinating hemoptyses of 500 to 1000 cc were erroneously attributed to pulmonary infarctions The bleeding was found to be due to bronchiectasis of the left lower lobe secondary to bronchostenosis caused by the pressure of a huge left atrium

Hemoptysis may occur repeatedly with moderate pulmonary engorgement and be absent when pulmonary stasis is severe Usually however it is more likely to occur with increasing pulmonary congestion In the cases reported by Oppenheimer and Schwartz

the attacks of hemoptysis were preceded by aura with psychogenic manifestations and pain between the shoulder blades The hemoptyses are not in themselves fatal and subside within a few days but the ultimate prognosis in these cases is usually poor Hemoptysis has been attributed to the rupture of small congested capillaries or small vessels in the lung (pulmonary "apoplexy") But according to Ferguson et al [8] the bleeding arises from the rupture of varices of the bronchial veins These varices result from pulmonary congestion and consequent enlargement of the communications between the pulmonary and bronchial veins Hemoptysis may also be due to pulmonary embolization and infarction This usually occurs in patients with severe pulmonary stasis right heart failure and atrial fibrillation

Cough is a frequent symptom It is usually worse at night and after physical exertion As a rule it is due to pulmonary congestion and occasionally in part to pressure of a large left atrium on the bronchial tree Occasionally cough is the most prominent symptom of the disease Most often the cough is non productive, but sometimes there is an associated mucoid or mucopurulent expectoration due to secondary bronchial and pulmonary infections which are prone to complicate pulmonary congestion in mitral stenosis The sputum frequently contains numerous "heart failure" cells

Acute pulmonary congestion or edema occurs in mitral stenosis but it is much less frequent than in aortic valvular lesions Nevertheless it is characteristic for patients with tight mitral stenosis to suffer from recurrent attacks of acute pulmonary edema with severe dyspnea orthopnea and the expectoration of frothy, blood stained sputum [27, 15] Pulmonary edema may occur in patients with atrial fibrillation or with sinus rhythm The occurrence of the attack is less sharply limited to the night and the horizontal position than in cardiac "asthma" due to left ventricular failure As a rule it follows sudden or severe *exertion emotional excitement, sexual intercourse* or bathing and may develop during operations, pregnancy, childbirth or after rapid digitalization It has also been precipitated by attacks of paroxysmal tachycardia or atrial fibrillation or by the intravenous administration of salt solution, premenstrual fluid retention infections of the upper respiratory tract, pulmonary embolism, hyperthyroidism or acute anemia

The most plausible explanation for its occurrence is the sudden intensification of pulmonary stasis in an already congested lung owing to an increase in venous return to and output from the right heart This serves to increase the pulmonary capillary pressure which rises significantly above the colloid osmotic pressure and results in transudation of plasma fluid into the pulmonary alveoli [4] A relatively competent right heart appears essential to its development The development of pulmonary edema due to a rise in pulmonary capillary pressure is favored also by factors increasing the resistance to flow in the left atrium, notably tachycardia, which shortens diastole during which the left atrium must be emptied The occurrence of paroxysmal dyspnea and pulmonary edema has been correlated with the height of the pulmonary capillary pressure, in those subject to these attacks the pressure is usually between 25 and 35 mm Hg at rest and higher with exercise [106] Occasionally a very elevated pulmonary capillary pressure has been found in patients who do not suffer from pulmonary edema This may be due to an inability of the right ventricle to increase its output with exercise, to a high pulmonary arteriolar resistance, which bears the brunt of the increased right ventricular output and "protects" the pulmonary capillaries, or to thickening of the pulmonary capillary alveolar membrane which impairs permeability and inhibits transudation of plasma despite a high capillary pressure [5] That acute pulmonary edema occurs so much less frequently in the pulmonary congestion of mitral stenosis than in that of left ventricular failure may be due to the more gradual development of pulmonary congestion in the former and consequently to differences in pulmonary accommodation Diminished permeability of thick capillaries may be a factor

Angina Pectoris Vague precordial sticking or aching sensations occur occasionally in *mitral stenosis Most often they are due to* extracardiac causes or to a superimposed neurosis Definite angina pectoris with typical precordial and arm radiations occurs occasionally and is probably due to associated aortic or coronary artery disease [131] Cardiac pain was present in 34 (8 5%) of 400 patients with mitral stenosis [2]

Hoarseness and paralysis of the left recurrent (laryngeal) nerve were first described by Ortner[196] in two cases of mitral stenosis The hoarseness may be intermittent at first Later it becomes constant and may progress to complete aphonia The most plausible explanation of this symptom appears to be that of Fetterolf and Norris [■] who concluded from detailed anatomic studies that the left recurrent nerve is compressed between the dilated left pulmonary artery and the aorta or aortic ligament Paralysis of the laryngeal nerve and left vocal cord also occurs in other cardiac conditions associated with dilatation of the pulmonary artery[66] The paralysis of the vocal cord is reversible since it may disappear following mitral commissurotomy[6]

Dysphagia is an uncommon symptom resulting from pressure of a dilated left atrium on the esophagus[231]

Weakness ■ a common complaint in mitral stenosis with failure just as it ■ in other forms of valvular disease It may be related to the excessive work of respiration or to an inadequate cardiac output *Menstrual disturbances* especially irregularity oligomenorrhea or amenorrhea are frequently encountered in women with mitral disease

Arrhythmias occur frequently both in this stage and when the right ventricle fails *Atrial fibrillation* is the most important of these De Graff and Lingg[68] encountered it in 43 per cent of 644 patients with mitral stenosis who were followed to their termination It was present in 42 per cent of 200 cases operated on for mitral stenosis[233] Its development ■ denoted symptomatically by palpitation less often by precordial distress and dyspnea It may be preceded by other irregularities such as extrasystoles or atrial flutter The fibrillation may be paroxysmal or persistent Usually paroxysmal fibrillation is converted into the permanent form It may herald the onset of right heart failure or it may actually precipitate it There is evidence that the cardiac output is diminished 20 to 25 per cent when atrial fibrillation occurs in patients with mitral stenosis[150] On the other hand clinical experience indicates that usually cardiac efficiency is not appreciably better with normal rhythm than with atrial fibrillation provided the ventricular rate can be kept slow Atrial fibrillation like right heart failure is a late stage in mitral stenosis Atrial fibrillation with slow ventricular rate is compatible with five or more years of life

Paroxysmal tachycardia and extrasystoles are seen frequently in patients with mitral stenosis but they are not characteristic of this lesion as is atrial fibrillation

3 Stage of Right Sided Heart Failure

Right heart failure is a common termination of mitral stenosis The longstanding increase of pressure in the pulmonary circulation as indicated anatomically by severe sclerosis of the pulmonary vessels leads to dilatation and hypertrophy of the right ventricle Failure of this chamber results in part from the mechanical effect of the increased strain and in part from the myocardial disease which is generally of rheumatic origin The precipitating causes have been discussed elsewhere (p 137)

The symptoms of right heart failure may develop gradually or suddenly Usually they follow a period dominated by symptoms of pulmonary engorgement Exertional dyspnea becomes more severe and breathlessness ■ present even at rest Orthopnea may be a prominent symptom Not infrequently when right sided failure is well developed the dyspnea and orthopnea are alleviated owing to the diminished right ventricular output into the pulmonary circulation But when severe changes in the lungs are fully established as a result of longstanding mitral stenosis the dyspnea and orthopnea may remain unabated even when the right ventricle fails Cyanosis similarly persists with the development of right-sided heart failure

Certain additional symptoms are intrinsic in right sided heart failure and result from engorgement of the systemic venous system (Chapter 7) These include engorgement of the cervical and other superficial veins enlargement of the liver peripheral subcutaneous edema and transudates in the serous cavities

Atrial Thrombosis Atrial (mural) thrombi may occur at any stage of mitral stenosis but they are especially frequent after right heart failure and atrial fibrillation develop[144, 28] These antemortem clots depend chiefly on the stagnation of blood in a very large atrium but rheumatic endocardial lesions may predispose to their formation[109] The thrombi are found in either atrium and especially in the atrial appendages In the absence of right heart failure and consequent dilatation of the right

atrium, the thrombi are usually confined to the left atrium They occur as small brownish-red ovoid masses of organized platelet thrombi attached to the pectinate muscles and endocardium Occasionally they are large spherical or polypoid purplish masses with smooth surface and gelatinous structure which partially or completely fill the atrial chamber At operation thrombi were found much more frequently in cases of pure mitral stenosis (86 of 200) than in cases of mitral stenosis with significant regurgitation (4 of 47 cases)[133] Perhaps the regurgitant jet inhibits stasis and thrombus formation Correspondingly arterial embolism was encountered in only 6 4 per cent of 47 cases of mitral stenosis and regurgitation as compared with 23 [illegible] per cent of 200 operated cases of pure mitral stenosis Actis Dato et al[14] reported the occurrence of thrombi in the left atrium in 56 (11 2 per cent) of 500 patients with mitral stenosis in whom valvulotomy was performed They were found in 35 3 per cent of the 133 patients with atrial fibrillation and in only 2 4 per cent of the 367 patients with sinus rhythm The left atrial appendage was thrombosed in 30 per cent of 1200 patients operated on by Bailey s group for mitral stenosis and in 53 per cent of those with persistent atrial fibrillation

Clinical symptoms are not an invariable consequence of the atrial thrombi which may be accidentally discovered post mortem Frequently however they produce serious clinical disturbances either by (1) embolic closure of distant vessels or (2) local obstruction of the stenotic mitral orifice

1 Embolization[144, illegible] Fragmentation or erosion of atrial thrombi results in dissemination of small particles which produce embolic closure of pulmonary cerebral, visceral or peripheral arteries De Graff and Lingg[65] found that embolism and infarction were somewhat more frequent among patients with atrial fibrillation Among 194 patients with rheumatic heart disease complicated by systemic emboli Daley et al [illegible] found a mitral lesion in 97 per cent atrial fibrillation in 90 per cent and either a mitral lesion, atrial fibrillation or both in 100 per cent About half of systemic emboli are cerebral[145] Pulmonary emboli with infarction of the lung occurred in almost half of the patients I have seen with mitral stenosis and right heart failure In these cases the source of the emboli may be thrombi either in the right atrium or in the peripheral deep veins of the lower extremity Pulmonary infarction is one of the complications to be considered when cardiac failure does not yield to treatment Systemic arterial emboli arise in left atrial thrombi Such emboli had occurred preoperatively in one quarter of 56 patients who were found to have left atrial thrombi at the time of mitral valvulotomy[14]

Several times I have observed the sudden occurrence of cerebral emboli in well compensated patients with mitral stenosis I have also seen cerebral embolization as the first clue to the presence of mitral stenosis Frequently the right middle cerebral artery is occluded with resultant aphasia and crossed hemiplegia Sometimes these hemiplegias are relatively benign in that they clear up with only slight disability in the patient But they are usually forerunners of further embolization A small cerebral artery may be occluded and only a focal paralysis or isolated aphasia is observed

Visceral embolization is not infrequent especially in the kidney and spleen Infarcts in these organs are most often discovered accidentally post mortem but clinical symptoms may occur I have also seen embolization of the hepatic artery with infarction of a lobe of the liver Of greater clinical importance is embolization of a mesenteric artery with infarction of the intestinal wall I have twice seen patients with infarction of the ileum operated upon for suspected acute appendicitis

Embolization of peripheral arteries is not rare Usually it produces dramatic clinical symptoms because of the abruptness of the occlusion and the absence of adequate collateral circulation Embolization of the aorta with formation of a pantaloon thrombus at its bifurcation may cause sudden sharp pain in the abdomen, lower back and extremities loss of pulsation and warmth of the lower extremities and shock More localized symptoms occur with embolization of the popliteal femoral or brachial arteries Gangrene may result and amputation may be necessary Occasionally recovery follows such amputation, but usually the general condition of the patient or subsequent emboli in other parts of the body cause death I have frequently seen spontaneous recovery from peripheral embolization without the development of gangrene

2 Ball Valve Thrombus The large ball shaped thrombi may completely occlude the

mitral orifice[60, 61] and produce sudden death I have also seen occlusion occur more gradually and lead to distinctive clinical features which make possible an antemortem (usually preterminal) diagnosis of this complication The patient develops a cadaveric mottled cyanotic discoloration of the hands and feet The ends of the extremities the tip of the nose and the ear lobes become cold and streaked with blue and undergo local necrosis The pulse may be weak or absent Within a few days the patient goes into shock and dies I have seen the identical clinical picture preterminally in patients with extremely tight mitral stenosis without the association of a ball valve thrombus All the patients with surface of the precordium in the region of the apex

A palpable *shock* may accompany the first sound at the apex and the second sound in the pulmonic area A systolic lift is often felt in the third left interspace over the outflow tract especially when pulmonary hypertension is moderate or severe [69] A similar systolic heaving pulsation in the left sternal and central precordial region[70] and sometimes in the epigastrium[71] is associated with right ventricular hypertrophy and clockwise rotation of the heart on its longitudinal axis In addition one can sometimes feel a *tap* in the apical region immediately after the second sound This is the palpable equivalent of the

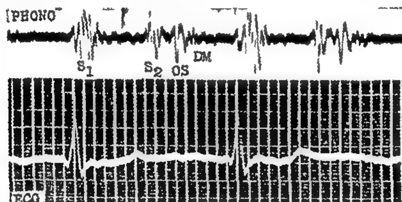


Fig 110 Mitral stenosis Opening snap (OS) with diastolic murmur (DM) Absence of presystolic murmur related to atrial fibrillation

ball valve thrombus studied by Schwartz and Biloon [68] had atrial fibrillation with rapid ventricular rate and were refractory to digitalis

Occasionally there is intermittent occlusion as the thrombosis is floated away from the orifice either by the blood stream or by change in the patient's position With recurrent occlusion there is an exacerbation of symptoms especially dyspnea and cyanosis syncope and sometimes disorientation convulsions or transient shock Relief may occur spontaneously Sometimes the patient learns to obtain relief by sitting up and leaning forward

Physical Signs in the Heart

Inspection In children the precordium may bulge There may be a visible pulsation in the epigastrium and to the right of the sternum if right ventricular hypertrophy has occurred

Palpation A characteristic *presystolic thrill* may be felt as a purring sensation on the sound produced by the opening snap of the rigid stenotic mitral valve (see below)

The apical impulse is usually felt at its normal site as a hurried slapping stroke A tentative diagnosis of mitral stenosis can sometimes be made on palpation which may reveal a rapid slapping apical impulse a presystolic thrill a diffuse precordial heaving pulsation and a palpable shock over the pulmonary region and apex

Percussion Prominence of the pulmonary artery and left atrial appendage may cause increased cardiac dullness along the left border at the level of the third interspace and fourth rib

Auscultation The auscultatory signs of mitral stenosis are frequently confusing because they vary greatly with the severity of the lesion at different stages of the disease Over long periods of time they may alter considerably even in the same patient because

the valve may be undergoing progressive change as a result of recurrent inflammation and healing

The characteristic sign is a localized apical *diastolic murmur* (Fig 120)[181] This may be entirely presystolic in time or it may fill most or all of diastole, with accentuation in presystole (Fig 120) or it may occur in the early or middle period of diastole and completely lack a presystolic element Most often it is predominantly mid-diastolic or predominantly presystolic in time The presystolic accentuation may disappear with atrial fibrillation or heart failure (Fig 119) The diastolic murmur arise as a result of an extremely rapid blood flow past the mitral obstruction into the left ventricle It occurs during those portions of diastole when the pressure difference between the left atrium and left ventricle becomes especially high This pressure difference is accentuated by atrial contraction, especially when the left atrium undergoes compensatory dilatation and hypertrophy

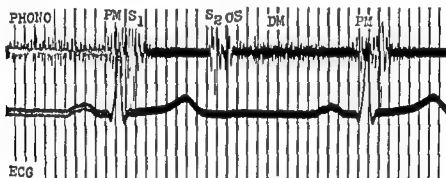


Fig 120 Mitral stenosis Opening snap (OS) and decrescendo diastolic murmur (DM) followed by crescendo presystolic murmur (PM)

The *presystolic murmur* which in itself suggests the diagnosis of mitral stenosis, is low pitched and rumbling or rolling in quality, with a characteristic crescendo accentuation which merges into a "snappy" or booming first sound This murmur is sometimes described as a mid diastolic roll with presystolic accentuation Graphic registration of the heart sounds indicates that the crescendo effect is not part of the murmur itself but only an auditory illusion created by the proximity of the murmur to the subsequent sharp first sound[163] The murmur is usually well localized just within the apex in an area which is not much larger than the bell of a Bowles stethoscope Thus it can be easily overlooked unless the region of the apex is completely examined Its small area of audibility corresponds to the small portion of left ventricle applied to the chest wall, while its radiation toward the left atrium is not heard, since that chamber is situated posteriorly deep in the chest wall Often the presystolic murmur is heard only if the patient is in the left lateral position Sometimes it is demonstrable only if the cardiac rate is quickened by exercise, emotion or the administration of amyl nitrite

The characteristic presystolic murmur is often absent in mitral stenosis On the other hand its presence does not always signify that lesion[170]

1 It is absent in mild cases, or early in the disease when the obstruction is relatively insignificant It disappears in the late stages of mitral stenosis if atrial fibrillation sets in or when the left atrium becomes extremely dilated The early diastolic murmur however, remains and occupies a variable part of diastole The diastolic murmur may be misinterpreted as presystolic in cases with atrial fibrillation if the ventricular rate is rapid and the murmur is close to the first heart sound

2 A typical presystolic murmur may be encountered in aortic insufficiency with a normal mitral valve[91] (Austin Flint murmur, p 689) Bland White and Jones[8] noted that a rumbling mid diastolic or presystolic murmur occurred in children and young adults with recent severe active rheumatic carditis and ventricular dilatation in whom post mortem examination revealed no mitral stenosis A presystolic murmur has been described also in some cases of severe secondary anemia and cardiac dilatation due to ancylostoma (hookworm) infection[113] and in cases of pernicious anemia and sickle cell anemia (Chapter 43) A transient mid

diastolic apical murmur has been noted in some cases of acute nephritis with hypertension and left heart failure[204] An apical diastolic murmur may occur in atrial or ventricular septal defect or patent ductus arteriosus[139]

A *systolic murmur* is commonly heard in cases of mitral stenosis[39, 18] and occasionally is the only murmur It may be due to an associated significant mitral insufficiency but it may be heard in pure mitral stenosis perhaps as a result of calcification of the cusps[43] It may also be due to an associated tricuspid insufficiency

The *first sound* at the apex is almost as characteristic as the presystolic murmur It is short somewhat delayed snapping (or snappy), loud and booming and accompanied by a palpable apical shock The first sound normally occurs within 0 06 second of the onset of the QRS In mitral stenosis it is usually delayed to 0 07 second or more[119] It is usually an early sign and may be noted before there is any diastolic murmur Its shortness and loudness have been explained as being due in part to the fibrotic changes in the valve cusps and chordae tendineae but especially to the rapid contraction of the left ventricle (as a result of the abbreviation of systole) A similar booming first sound may be heard in Graves' disease where there is diminished ventricular filling due to tachycardia When the mitral valve becomes completely rigid and immobile the sharp first sound disappears (as does the opening snap)

The time interval between the onset of the QRS of the electrocardiogram and the first sound in the phonocardiogram was found to vary according to the duration of the preceding cycles[18] Wells[39] devised a method whereby the severity of the mitral stenosis could be estimated from a logarithmic phonocardiogram and a synchronous electrocardiogram He measured the Q 1 interval (onset of QRS to onset maximal vibration of first heart sound) the 2 O S interval (onset of second sound to opening snap) and the R R interval The Q 1 and 2 O S intervals were corrected to correspond to a cycle length of 0 8 second The severity of mitral stenosis was estimated from the difference between these intervals. The more rigid the mitral cusps the more the delay between the onset of QRS and the first sound the higher the atrioventricular gradient the less the interval between the second sound and the opening snap Therefore, the more severe the mitral stenosis the greater the difference between these two intervals (Q 1)-(2 O S)

The *second sound* heard over the pulmonic area is accentuated regardless of the degree of pulmonary hypertension Like the first sound at the apex it may be accompanied by a palpable shock usually only in cases with moderate or severe pulmonary hypertension (i e mean pulmonary artery pressure over 40 mm Hg)[43] The accentuated pulmonic second sound is due partly to the rise of pressure in the pulmonary artery and partly to the rotation of the pulmonary artery and conus, which brings them closer to the chest wall The pulmonic second sound may be *reduplicated* as well as accentuated The pathogenesis of this reduplication is uncertain but may be the change in the relative pressures in the pulmonary artery and aorta with resulting asynchronous closure of the semilunar valves Reduplication of the second pulmonic sound with accentuation of the second element of the split sound has been correlated with severe pulmonary hypertension[43]

The *second sound at the apex* may appear reduplicated since it is often followed immediately by a click which is palpable as well as audible This is caused by the sudden recoil of the resistant mitral cusps as they are opened by the strong atrial stream It has been termed the "opening snap or the claquement d ouverture of the mitral valve (Figs 119 120)[167] While it has long been recognized by continental writers its frequent occurrence was emphasized in this country by Margolies and Wolferth[172] who made detailed phonocardiographic studies They demonstrated that this third apical sound (opening snap) occurred usually between 0 08 and 0 11 second after the beginning of the second sound which confirms the concept that it is connected with the opening of the mitral valve The opening snap occurs at the peak of the V wave in the venous pulse tracing The briefer the interval between the second sound and the opening snap the higher the atrioventricular gradient and the more severe the stenosis In the presence of atrial fibrillation the interval between the second heart sound and the opening snap of the mitral valve varies with the preceding cycle length But when mitral regurgitation is associated, the interval may remain fixed[154] This extra click may be

quite loud and produce an echo effect which the French have termed "bruit de rappel" The opening snap may be misinterpreted as a normal third heart sound as a gallop rhythm or as a split second sound

The second component of the split second sound occurs earlier than the opening snap, whereas a third heart sound occurs later The opening snap is high pitched and sharp, the third heart sound is low pitched and dull The occurrence of an extra sound at the apex in a young individual without failure and especially with a history of rheumatic fever should always suggest the possibility of mitral stenosis

Functional Pulmonic Insufficiency In addition to the apical diastolic murmur in mitral stenosis described above a soft, blowing high pitched diastolic murmur is heard over the pulmonic area in cases with severe pulmonary hypertension This was described in 1889 by Graham Steell as "the murmur of high pressure in the pulmonic artery" and is known as the Graham Steell murmur[2 3] It is probably the result of a functional insufficiency of the pulmonic valve due to pulmonary artery hypertension and consequent dilatation of that vessel and of the pulmonic orifice Rheumatic inflammation of the base of the pulmonary artery and valve and athero sclerotic changes in the vessel may play an accessory role in its dilatation While relative pulmonic insufficiency and the Graham Steell murmur are encountered most often in mitral stenosis, they may also occur in various chronic pulmonary diseases associated with increased pressure in the pulmonary circuit The Graham Steell murmur must be distinguished from the diastolic murmur of aortic insufficiency The latter is characterized by differences in the roentgenologic appearance of the heart the associated electrocardiographic findings of left ventricular hypertrophy, and sometimes by distinctive peripheral signs (p 690)

Pulse and Blood Pressure in Mitral Stenosis

In compensated mitral stenosis the *pulse* is generally normal In extreme stenosis, the pulse may become soft and small, corresponding to a diminished stroke output Late in the disease especially during the stage of right sided heart failure the pulse is often completely irregular due to atrial fibrillation Extrasystoles and dropped beats are not infrequent at various stages of mitral stenosis

The *blood pressure* in mitral stenosis is e normal or slightly diminished The pulse p sure may also be somewhat less than nor The occasional reduction in blood pres and pulse pressure probably reflects slightly diminished stroke output Main ance of blood pressure despite a dimini cardiac output has been ascribed to a c pensatory vasoconstriction

With advancing age, patients with m stenosis were said to develop *hyperten* more frequently than control groups[24] H ever, this alleged relationship has b doubted[206 113] Hypertension was noted 16 5 per cent of 200 patients with m stenosis[113] The hypertension modified cardiac signs and electrocardiographic f ings usually associated with mitral steno

The Pulmonary Blood Pressure Pulmon Hypertension This has been discussed 649) The presence and degree of pulmon hypertension are important in the selectio patients for mitral commissurotomy a favorable results are not likely in patients w little or no pulmonary hypertension Since t can be determined directly only by card catheterization attempts have been made estimate it by correlation with clin phenomena[243] A Graham Steell murmur, *palpable* second pulmonic heart soun prominent atrial 'a' waves in the jugu venous pulse, very prominent pulmon arteries on roentgen ray examination of t chest and electrocardiographic evidence right ventricular hypertrophy are associat with moderate or severe pulmonary hyp tension Nocturnal dyspnea and hemopty occur more commonly with moderate or seve pulmonary hypertension than with mild h pertension but cannot be used to ass ess t degree of pulmonary hypertension in a given patient

Roentgenologic Appearance of the Heart Mitral Stenosis

The roentgenologic appearance of the hea in mitral stenosis varies with the stage severity of the lesion

1 In cases of early or mild mitral stenos the cardiac size and outlines are often no mal[198] If some left atrial dilatation a hypertrophy are present they are difficult demonstrate

2 More advanced cases reveal evidence enlargement of the left atrium and o casionally of the right ventricle[148]

(a) Left atrial enlargement (p 103) is characterized by encroachment on the retrocardiac space and posterior displacement of the barium containing esophagus as seen in the right anterior oblique view (Fig 41*B* p 104) Recent studies suggest that the size of the left atrium is estimated best by a left lateral teleoroentgenogram with barium in the esophagus [135]

(b) In the posteroanterior view the left *sided waist of the heart is filled out there is a* straightening or convexity of the left middle cardiac contour due to enlargment of the left atrial appendage and increased prominence of the pulmonary artery and its left main branch (Figs 41*A* p 101 and 122) The latter results chiefly from elevation and elongation of the pulmonary artery [114] by the left atrium and enlarged right ventricle and slightly from dilatation of the artery The prominence of the atrial appendage is below that of the pulmonary artery This straightened or convex left border gives the cardiac silhouette its so-called mitralized configuration But a similar appearance may be encountered in other conditions associated with pulmonary hypertension When the left atrium is extremely large it may form a second bulge on the right border just above the right atrial segment or it may rarely form the entire right cardiac border (Fig 43 p 105) The enlarged hypertrophied left atrium may appear as an increased density within the shadow of the heart In the posteroanterior view the barium containing esophagus is seen to be displaced to the right (Fig 42 p 104) The left main bronchus is elevated toward the horizontal position (Figs 42 and 43 pp 104 and 105)

(c) In the left oblique view the enlargement of the left atrium causes upward and backward displacement of the upper posterior cardiac contour and may splay the main bronchus and compress and elevate the left one Displacement of the right chambers by the large left atrium may cause an enlargement of the cardiac shadow to the right and anteriorly in this view

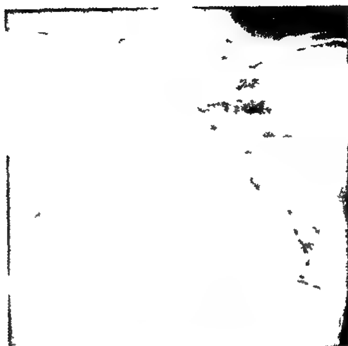
Right ventricular enlargement is not prominent and may be revealed by anterior encroachment on the retrosternal space in the right lateral view The aortic knob is small in contrast with the prominent pulmonary artery

3 With advanced mitral stenosis and heart failure the above alterations become accentuated In addition the right cardiac border is displaced to the right by enlargement of the right atrium or by displacement of this chamber by the enlarged right ventricle and left atrium The left cardiac border may also be displaced to the left by enlargement and rotation of the right ventricle which may come to form the apex of the heart (Fig 121) The transverse diameter of the heart is enlarged

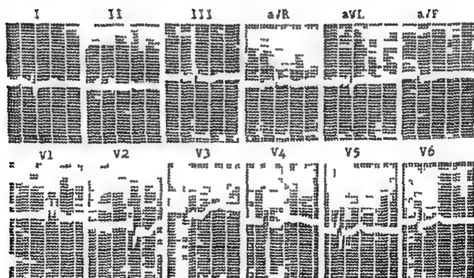
4 Calcification of the mitral valve may be demonstrated on a slightly overpenetrated film of the chest preferably by spot films after fluoroscopy to localize the site of calcification Genovese and Levine[47] thus demonstrated calcification of the mitral valve in 15 or 50 patients with mitral valvular disease All but 3 of these 15 with mitral calcification were admitted for congestive heart failure In 10 of the 15 there was atrial fibrillation In general there was good correlation between mitral calcification and the severity of mitral valvular disease A similar correlation was not associated with aortic valvular calcification Valvular calcification may also be demonstrated by planigraphy [119] Janton and associates[186] reported the finding of calcification of the mitral valve in 65 per cent of 47 patients in whom there was mitral stenosis with associated regurgitation and in [illegible] per cent of those with pure mitral stenosis Calcification of the left atrium may also be observed roentgenologically [45, 130]

5 The pulmonary vessels especially at the hilum become more prominent and the pulmonary fields congested (Fig 122) Prominence of the main pulmonary arteries is a striking feature in tight mitral stenosis with severe pulmonary hypertension In such cases the radiologic appearance may resemble that of interatrial or interventricular septal defect with severe pulmonary hypertension The prominent perihilar vessels contrast with the narrow peripheral arteries

The pulmonary veins become enlarged especially the right inferior pulmonary vein Costophrenic septal lines [46] also termed lines B of Kerley [1] are horizontal lines hair line to 2 mm thick and about 2 or 2 5 cm long 5 to 10 cm above the costophrenic angle occurring in patients with pulmonary hypertension secondary to mitral stenosis usually when the mean pulmonary artery pressure is 39 mm Hg or higher[47] (normal 20 mm Hg)



A



B

Fig 191 *A* Pure mitral stenosis in 57 year old man Prominent pulmonary artery and left atrial appendage on left Large pulmonary vessels on right Enlarged lower left contour with elevated apex formed by hypertrophied and rotated right ventricle but misinterpreted as enlarged left ventricle because of basal diastolic murmur (due to pulmonary insufficiency but attributed to aortic insufficiency) and apical and lower sternal systolic murmur (due to tricuspid insufficiency but attributed to mitral insufficiency)

B Electrocardiogram of same patient showing right ventricular hypertrophy with incomplete right bundle branch block No evidence of associated left ventricular hypertrophy

They are better seen on the right than on the left side, and there may be only 2 or 3 lines or as many as 10 to 15 spaced 0.5 to 1.0 cm apart. The lines are thought to represent widening of the interlobular septa by edema fluid.[III] Occasionally there is an acute increase in the degree of pulmonary congestion with consequent pulmonary edema (Fig. 123). Pulmonary infarction occurs commonly (Fig. 121). In longstanding cases of

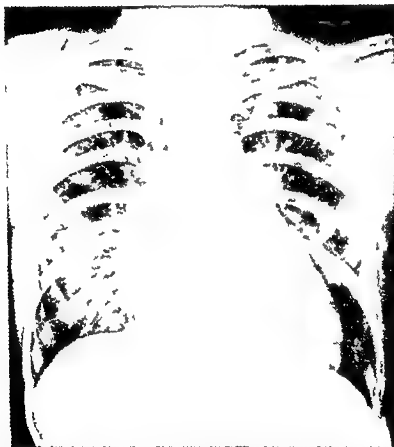


Fig. 122 Mitral stenosis. Prominent left pulmonary segment. Large hilar and pulmonary vessels. Chronic pulmonary congestion with finely mottled or nodular densities in both lung fields. Limited cardiac reserve but no overt physical or other signs of heart failure.

mitral stenosis and pulmonary congestion hemosiderin deposits produce nodular densities or reticular areas resembling miliary tuberculosis, sarcoidosis, pneumoconiosis or carcinomatosis[160, 95, 7, 8, 79] (Fig. 125). Sometimes these disseminated nodules are calcified or even ossified.[71]

The above configurations may be modified by associated lesions, notably by left ventricular enlargement in aortic insufficiency or to a lesser extent in mitral insufficiency.

Angiocardiography

Normally the left atrium is not clearly demarcated from the left ventricle. In mitral stenosis the opaque material is held up in the left atrium, which becomes sharply outlined for comparatively long periods.[50, 8] Angiocardiograms in patients with severe mitral regurgitation show enlargement of both the left atrium and ventricle without a sharp difference in opacification. However, other studies have failed to disclose angiocardiographic patterns which distinguished between mitral stenosis and mitral regurgitation.[219] The angiocardiographic diagnosis of left atrial thrombosis has been reported.[249a]

Cardiac Tomography (Planigraphy)

Section radiography may aid in distinguishing between mitral stenosis and mitral insufficiency by distinguishing right ventricular from left ventricular enlargement, since the right ventricle enlarges an



Fig. 123 Mitral stenosis with pulmonary edema. Diffuse haziness of lung fields with prominent pulmonary vessels and radiating streaks. Tendency to involve medial fields with clearing at periphery.

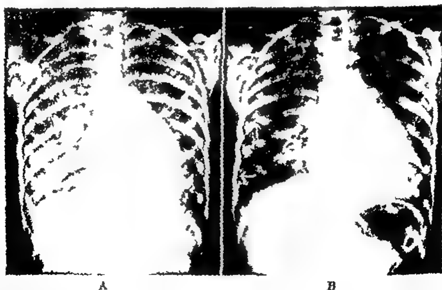


Fig. 124 *A* Mitral stenosis. Pulmonary infarction in right middle lobe with small pleural effusion. Upper border of infarct delimited by transverse fissure.

B Three months later. Infarct cleared. Residual thickening of right transverse fissure (upper arrow) and vertical band of pleural thickening along lower right chest wall (lower arrow).

teriorly and the enlarged left ventricle occupies posterior sections Thus the bulk of the enlarged cardiac shadow is anterior if it involves the right ventricle posterior if it involves the left ventricle Body section radiography has also been used to delineate a large left atrium[209] (Fig 4 p 8)

The Electrocardiogram in Mitral Stenosis

The P waves in leads I and II are often widened notched and may be of increased voltage presumably due to enlargement and hypertrophy of the left atrium and asynchronous atrial activation [3, 83] (Fig 50 1 p 119) The P waves in leads III and V_1 may be diphasic When P is diphasic in V_1 and the negative phase of P is deep and broad left atrial enlargement is suggested There is usually right axis deviation (vertical electrical axis) and often evidence of right ventricular hypertrophy [3, 83] (p 113) (Fig 47 p 110)



Fig 12a Hemosiderosis of the lung in mitral stenosis Dense miliary nodular opacities throughout both lung fields

Distinctive signs suggesting right ventricular hypertrophy such as a large R wave with or without a small s wave followed by an inverted T wave in lead V_1 (p 115) occur as a rule in cases with more severe degrees of pulmonary hypertension and right ventricular hypertrophy [3] Right ventricular hypertrophy may be indicated more regularly if right precordial leads such as V_{3R} and V_{4R} are taken Occasionally there is evidence of right bundle branch block [203] Atrial fibrillation is frequent in advanced cases There may be occasional atrial premature beats If aortic valvular disease is associated there may be no axis deviation or deviation to the left

The Vectorcardiogram in Mitral Stenosis

The vectorcardiogram may disclose evidence of both left atrial (p 122) and right ventricular hypertrophy (p 116) It distinguishes the latter from mere rotation of the heart and especially from right bundle branch block [213] In severe mitral stenosis with right ventricular hypertrophy the mitral segment of the QRS loop in the horizontal plane is directed counterclockwise and the loop is deviated to the right In the frontal plane the loop is more vertical than usual

The Ballistocardiogram

A distinct deformity was described by Davis et al [6] This consisted of a presystolic headward wave followed by a more constant footward deflection which precedes the I and occurs 0 10 second after the electrocardiographic Q The footward wave is later than the G and deforms the H wave by lowering its amplitude or abolishing it The I wave is distorted and its inscription delayed That this abnormality is specific for mitral stenosis could not be confirmed by Izak and Braun [134]

Complications of Mitral Stenosis

These occur so frequently that they have been described as features of the disease For convenience they are recapitulated here

(1) Cardiac failure (2) atrial fibrillation (3) atrial thrombosis and arterial embolization (4) subacute bacterial endocarditis (5) bronchopulmonary infections (6) laryngeal nerve paralysis (7) dysphagia In later years mitral stenosis may be complicated by hypertension and coronary atherosclerosis

Rokitansky [60] first stressed that pulmonary tuberculosis is very uncommon in cases of mitral stenosis because of the protective action of pulmonary congestion but this classic belief has been repeatedly questioned [60]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF MITRAL STENOSIS AND MITRAL INSUFFICIENCY

The diagnosis of mitral stenosis depends on recognition of the characteristic diastolic presystolic murmur in association with roentgen ray evidence of a large left atrium or a mitralized heart If the murmur is typical the diagnosis is justified even if there is no demonstrable enlargement of the left atrium The diagnosis is supported by a history of rheu

matic fever or by fluoroscopic demonstration of calcium in the mitral valve cusps It should be reemphasized that the typical presystolic murmur may be absent if there is atrial fibrillation or a huge, dilated left atrium But the apical diastolic murmur usually persists Other diagnostic signs suggesting mitral stenosis are the sharp snappy first sound at the apex the "opening mitral snap" following the second sound at the apex and a diastolic thrill Electrocardiographic records showing right axis deviation large, notched P waves and atrial fibrillation also suggest mitral stenosis especially if there is a history of rheumatic fever

A major diagnostic problem has been encountered in determining whether a significant mitral insufficiency is associated with mitral stenosis or whether the insufficiency is the predominant lesion This is a problem because mitral regurgitation is not yet consistently amenable to surgical therapy and an unnecessary exploratory thoracotomy and cardiotomy may seriously impair the clinical course or result in a fatality When a satisfactory surgical procedure is available, diagnosis of associated or predominant mitral regurgitation will be less important Then, if mitral valvular disease is diagnosed and there is a clear indication for its surgical treatment, a thoracotomy may be performed and the procedure chosen can be adjusted to the type of mitral valvular disturbance

There is usually no problem in the large majority of cases of "pure" mitral stenosis in which the characteristic mid-diastolic and presystolic murmur, sharp first sound opening snap and electrocardiographic evidence of right ventricular hypertrophy are diagnostic The presence of an apical systolic murmur as well as a diastolic murmur is the usual basis for considering the possibility of a significant regurgitation as well as mitral stenosis But Janton et al[138] reported such a combination of systolic and diastolic murmurs in 30 per cent of 200 patients in whom "pure" mitral stenosis was found at operation The louder the systolic murmur, the more prolonged it is, especially if it replaces the first sound lasts throughout systole and encroaches on the second sound, the more likely it is to be due to mitral regurgitation A loud sharp first sound and the presence of an opening snap indicate that the systolic murmur is not due to significant mitral regurgitation

A number of other findings are commonly associated with mitral regurgitation but too many exceptions make them unreliable for application to the individual case[234] Among these usually corroborative findings are systolic expansion of the left atrium, as determined by fluoroscopy or electrokymography, very great enlargement of the left atrium, and an exaggerated systolic (regurgitant) V wave or plateau in pressure tracings obtained by a catheter wedged into a pulmonary "capillary", by a balloon in the esophagus at the level of the left atrium,[158] [11] or more directly by needle puncture of the left atrium through the chest wall,[30] [178] suprasternal notch[202] or bronchoscope[30] Bateman and January[21] found that the time of onset of the intrinsicoid deflection (peak of R wave) in V_5 or V_6 occurred later and the voltages of R in V_5 or V_6 and of S in V_1 were greater in mitral regurgitation than in cases of mitral stenosis Cardiac tomography and angiocardiography (p 663) may be useful in differentiating mitral stenosis from mitral insufficiency, but these procedures are not generally used Cardiac catheterization has been used to estimate the size of the ventricles in mitral valve disease[207] In practice, the most reliable finding indicative of mitral regurgitation is the presence of left ventricular hypertrophy as disclosed by the electrocardiogram especially the precordial leads (p 645 and p 111) when associated with a loud prolonged, apical systolic murmur But there must be no other disease such as severe hypertension or aortic valvular disease to account for the left ventricular hypertrophy

Recent studies with indicator dilution curves suggest that these may be used to distinguish between mitral stenosis and mitral regurgitation Conn et al[5 a] catheterized the left side of the heart by direct atrial puncture and made multiple radiopotassium (K^{42}) injections consecutively into the left atrium left ventricle and aorta of patients with mitral valvular disease Successive blood samples were drawn from the femoral artery and analyzed for radioactivity The findings in mitral stenosis differed from those in mitral regurgitation in that the atrial circulation time was longer than the ventricular, and the atrial total volume was increased while the ventricular volume was normal in mitral stenosis Following the injection of dye into the left atrium or ventricle of patients with

mitral insufficiency a disproportionate prolongation of the disappearance slope was observed in dilution curves recorded at the radial artery[1,4,134] After injection of the dye through a catheter in the left ventricle there was a rapid appearance of the dye in the right atrium in the presence of mitral regurgitation[134]

Sometimes there is diagnostic difficulty in differentiating mitral stenosis with a Graham Steell murmur of pulmonic insufficiency from aortic insufficiency with a presystolic murmur thought to be an Austin Flint murmur (p 689) Or else there is a problem whether an inoperable aortic insufficiency is associated with an otherwise operable mitral stenosis because of the presence of a diastolic murmur at the base of the heart or whether the latter represents a Graham Steell murmur An Austin Flint murmur rarely if ever occurs except in the presence of left heart failure with left ventricular dilatation A sole or associated aortic insufficiency should be distinguishable by the characteristic boot shaped cardiac configuration due to left ventricular enlargement prominent pulsating aorta frequent peripheral vascular phenomena (p 690) and especially evidence of left ventricular hypertrophy on the electrocardiogram Mitral stenosis when associated with a Graham Steell murmur is especially likely to be associated with electrocardiographic signs of right ventricular hypertrophy

Occasionally the systolic murmur of aortic stenosis is heard best or only near the apex of the heart It is usually more harsh and more likely to be associated with a thrill than the systolic murmur of mitral insufficiency Furthermore the murmur of aortic stenosis is more likely to start later in systole and to be accentuated in mid systole does not include the first sound and rarely extends to the second sound The second aortic sound is likely to be weak or absent and calcification may be demonstrable in the aortic valve (p 704)

In the presence of tricuspid regurgitation an apical systolic murmur due to that valvular disturbance may be misinterpreted as mitral insufficiency when there is actually a pure mitral stenosis Electrocardiographic evidence of right ventricular hypertrophy and maximal intensity of the murmur in the tricuspid area with increased intensity on inspiration are diagnostically helpful

An apical diastolic murmur may be heard in conditions other than mitral stenosis (p 659) The crescendo murmur and/or the sharp first sound of mitral stenosis may be simulated in asthenic individuals with tachycardias of various origins in persons with Graves disease or with cardiac neurosis The atrial sounds in cases of 2 1 heart block may simulate a diastolic rumble Splitting of the first sound or audibility of the atrial sound may be mistaken for the low pitched presystolic murmur of mitral stenosis but the duration is much less than that of a true murmur An apical mid-diastolic murmur in the absence of mitral stenosis may be heard in early rheumatic fever and disappear later[8] Duplication of the second sound in young recruits has been described as simulating the signs of mitral stenosis[49] The pulmonic second sound is accentuated in children and young adults

The physician may mistakenly interpret the various pulmonary symptoms and signs in mitral valvular disease as indicating pulmonary tuberculosis or he may make a diagnosis of bronchopneumonia without recognizing the underlying valvular disease or complicating pulmonary embolization Paralysis of the left recurrent nerve may suggest the diagnosis of syphilitic thoracic aneurysm or bronchogenic carcinoma The observation of large hilar shadows due to the dilated pulmonary vessels in mitral stenosis with pulmonary hypertension has led to x ray therapy for lymphosarcoma and to operative intervention for neoplasm

Occasionally mitral stenosis may be caused by tumor and thrombi[61] Since these like rheumatic mitral stenosis may be amenable to surgical relief preoperative diagnosis of the etiology of the mitral stenosis is not essential

PROGNOSIS OF MITRAL VALVE DISEASE

Since mitral disease is essentially a consequence of rheumatic fever its prognosis and treatment will be discussed with rheumatic heart disease (page 849) While some statistical studies indicate that the type of valvular disease is not significant for prognosis others suggest that the outlook in mitral disease especially mitral stenosis is less favorable than in aortic valvular lesions of rheumatic origin The average age at death varies between 40 and 45 years but about 20 to 25 per cent survive the age of 50[11] There is evidence that an increasing number of patients with mitral

stenosis survive the age of 50[127] and I have seen many patients beyond the age of 60. In one series 65 patients with mitral stenosis seen between 1913 and 1946, 26 had died at an average age of 49.4 years and of those still alive the average age was 58 years.[165] Many individuals live a virtually normal life span, and engage in normal activities. Most women with compensated mitral stenosis are able to bear one or more children without serious consequences. However, pregnancy in a person with mitral stenosis is occasionally complicated by the onset of cardiac failure or subacute bacterial endocarditis and rarely by acute pulmonary edema or a dangerous form of chorea.

Wilson and Greenwood[249] have been investigating the natural life history of mitral stenosis as a basis for comparing the operative mortality with the prognosis under conservative treatment. They noted three milestones. The first was characterized by the onset of attacks of pulmonary edema, orthopnea or severe dyspnea on mild exertion (walking one block or climbing one flight of stairs); the second by the onset of atrial fibrillation and the third by the development of right heart failure. Death in six months in 16 per cent of the cases followed the first and second. Death occurred in six months in 25 per cent of those who developed right heart failure.

Persistence of rheumatic activity warrants an unfavorable prognosis. The prognosis is generally worse the larger the size of the heart, since the heart size usually reflects the severity of myocardial damage and the degree of cardiac failure. Persistent atrial fibrillation is usually a late stage with death likely to follow in three to five years. But in a series of 65 cases studied by Love and Levine[168] the average duration of atrial fibrillation was 12.8 years and of congestive heart failure 10.6 years. Most of the patients were still alive. Such data should be considered in trying to compare the risk of surgical operation for mitral stenosis with the outlook on conservative treatment. Left-sided failure with pulmonary congestion may be present for many years but the outlook is not as good as for patients who are perfectly compensated. Right heart failure is a serious omen but death does not ensue as rapidly as with right heart failure in aortic valve disease. Many patients live for three to five years or more after its onset, if proper treatment is employed. Embolization is almost always an unfavorable omen, especially since it is frequently associated with heart failure and atrial fibrillation. There is a 50 per cent mortality with cerebral embolism and an even higher mortality with embolism to the mesenteric artery.[illegible] Once embolization occurs it is usually recurrent. Of 79 patients who had a single embolic episode, there was an immediate mortality of 30 per cent.[58] But patients may live for five years or more after an embolus in mitral stenosis. Associated valvular disease usually enhances the seriousness of the condition because the more valves involved, the more serious is the myocardial injury. Statistical observations are in disagreement on this point. Associated cardiac disease, such as coronary atherosclerosis, also diminishes life expectancy, but clinical coronary disease usually occurs in patients who have already survived a relatively long time.

The cause of death is cardiac in 70 to 90 per cent of cases. Stone and Feil[24] found that 81 per cent died of circulatory failure. Bronchopulmonary infections are frequent causes of death, either directly or by contributing to the development or persistence of cardiac failure. Pulmonary, cerebral or visceral emboli often play an accessory or primary role in causing death. Subacute and acute bacterial endocarditis occur less frequently than in aortic insufficiency.

Favorable factors in prognosis are: absence of rheumatic activity; survival beyond adolescence; absence of symptoms and signs of either left or right heart failure, little or no demonstrable cardiac enlargement, and favorable economic and social status which permits the avoidance of undue physical and mental stress or climatic hazards and an intelligent attention to the laws of good hygiene.

SURGICAL TREATMENT OF MITRAL STENOSIS

The surgical treatment of mitral stenosis by mitral commissurotomy (mitral valvuloplasty)[9, 11, 122, 35] has become fairly standardized.[10, 54] Some of the imperfections of the surgical procedure would be overcome if it could be performed under direct vision and if severe mitral regurgitation previously present or produced by commissurotomy could be properly repaired.

Indications for Mitral Commissurotomy (Valvuloplasty)

The objective of the operation is to enlarge the narrowed mitral orifice Therefore it is indicated whenever a patient suffers intolerable or progressive symptoms which are believed to be due to the mechanical impediment of severe mitral stenosis

In selecting patients for mitral commissurotomy the physician must assess (1) the probable outlook with non surgical treatment (2) the operative mortality and (3) the probability of improved function and longevity as a result of the operation

At the present time we have more accurate information about items 2 and 3 than about item 1 The over all operative mortality is about 10 per cent but it may be only 3 to 5 per cent in the better risk cases falling in Group II or III of the New York Heart Association (p 157) and 25 per cent in the poor risk cases (Group IV) It also appears that if patients are carefully selected on the basis that their symptoms are probably due to an extremely narrowed mitral orifice and if a thorough mitral commissurotomy is performed about 75 per cent of operated patients or [illegible] per cent of those who survive will be relieved of their symptoms and will experience a good or excellent functional improvement (p 676) The presence of a significantly tight mitral stenosis is indicated by the symptomatology especially attacks of pulmonary edema with exercise recumbency respiratory infection and so on by the classic signs of mitral stenosis and the electrocardiographic pattern of right ventricular hypertrophy Catheterization and other special studies need be undertaken only in doubtful cases But studies with transthoracic suprasternal or bronchial left heart catheterization may greatly enhance our diagnostic skill and our ability to appraise surgical indications and to evaluate surgical effectiveness A significant mechanical impediment at the mitral valve is improbable if the pulmonary arterial and capillary pressure and the left atrial pressure are not definitely elevated An elevated left atrioventricular gradient is a direct measure of mitral obstruction Adequacy of the mitral commissurotomy is indicated by ability to admit two fingers held side by side and especially by demonstration of almost complete reduction of the atrioventricular gradient (by simultaneous measurement of left atrial and ventricular pressures) as soon as the commissurotomy is completed

The outlook with conservative treatment is the most difficult to estimate because of the variable course of the disease In practice classifying patients according to the functional standards of the New York Heart Association (p 157) the outlook with conservative treatment is regarded as best in Group I and poorest in Group IV It is generally agreed that mitral commissurotomy is not indicated in patients without symptoms i e those in Group I Nevertheless Bailey has operated on about 40 patients in Group I among over 1000 commissurotomies and found that these patients had a tight mitral stenosis and were benefited by the operation Although asymptomatic many of these patients had no symptoms only because of imposed limitations in activity Many of the patients in Group II have too mild symptoms to be selected for commissurotomy Other patients in Group II have disturbing symptoms which occur only with unusual stresses In such borderline cases whether to operate or not will depend in part on the patient s subjective reaction to his symptoms and on his way of life The married woman who does not have to work for a livelihood who has domestic employees to free her of household activities and has the use of an elevator indoors and a car or taxi outdoors may not regard her symptoms or disability as severe enough to justify even minimal risk of an operation On the other hand symptoms may be frequently induced and become disabling in the woman who must perform her own house work raise a family or hold a job or the man who is employed at work which demands considerable physical exertion

Progression and intensification of symptoms not acutely but over a period of many months or years is a strong indication for mitral commissurotomy Harken s group II[1-4] consists of patients who are handicapped by their symptoms which in contrast with those of his group III are static or not particularly progressive This group II corresponds to the worst cases of Group II and the less severe cases in Group III of the New York Heart Association The patients are clearly limited in activity by exertional dyspnea or fatigability experience occasional episodes of paroxysmal dyspnea and cough and may have atrial fibrillation but there is no evidence of

frank congestive heart failure Relatively few are operated upon, namely those who find their symptoms intolerable because of their subjective reaction or the nature of their required or desired activities Those who are not subjected to operation must be carefully observed for progression of symptoms which would transfer them to Harken's group III This corresponds roughly to Group III of the New York Heart Association and includes patients suffering from pulmonary symptoms (dyspnea fatigability or cough on exertion, hemoptysis orthopnea, paroxysmal dyspnea and especially pulmonary edema) which are progressive in nature and which handicap the patient by significantly and increasingly limiting his ordinary activities A large number of them have atrial fibrillation and some have suffered peripheral emboli These form the bulk of patients who are suitable for mitral commissurotomy and in whom it is clearly indicated i e, the anticipated benefit justifies the relatively small operative risk in view of the present disability and relatively unfavorable outlook with conservative therapy With further reduction in operative mortality and possible improvement in the results obtained, more and more patients in group II may also be encouraged to undergo the operation

Group IV of the New York Heart Association includes patients with symptoms of heart failure at rest Group IV of Harken is roughly identical but is defined to include patients who are severely incapacitated or bedridden, suffer from "chronic congestive heart failure", i e right- and left-sided heart failure with atrial fibrillation in the majority and with a higher incidence of peripheral emboli than in Group III Mitral commissurotomy is indicated in most of these patients even though the operative mortality is substantially higher and the chances of substantial functional improvement are less than in Groups II and III The operative outlook is better when the manifestations of heart failure can be greatly ameliorated by vigorous medical therapy

Despite the presence of right-sided heart failure one cannot assume that there are irreversible pulmonary arteriolar changes or right ventricular damage If the stenosis is relieved, the increased arteriolar resistance may diminish and right ventricular function may be restored, although a contrary opinion has been expressed[118] Except in preterminal cases, mitral commissurotomy may be indicated, despite high operative risk, because of extreme disability and the probability of an early demise without operation However persistent gallop rhythm despite adequate medical therapy is regarded as a contraindication A fair percentage of even the most disabled patients may be salvaged, occasionally with dramatic improvement The calculated risk of surgery and the limited chance of improvement must be explained to the patient's family, and weighed against the complete present disability and the poor prognosis with conservative therapy

Contraindications

Mitral commissurotomy should not be undertaken if the predominant valvular lesion is *mitral insufficiency* or *aortic insufficiency* until operative correction of these lesions is perfected The basal diastolic murmur of pulmonary insufficiency secondary to severe mitral stenosis should not be mistaken for that of aortic insufficiency (p 660) In essence, mitral commissurotomy is contraindicated currently in the presence of left ventricular hypertrophy unless this is due to an associated aortic stenosis One must be careful not to misinterpret right ventricular enlargement as left ventricular enlargement on the basis of a posteroanterior x ray film of the chest Tricuspid insufficiency associated with right heart failure is not a contraindication to commissurotomy although its presence, like that of advanced right heart failure per se, tends to increase the surgical risk and diminish the incidence of clinical benefit Tricuspid stenosis is no contraindication and if severe, should be repaired by tricuspid commissurotomy

Rheumatic activity is generally regarded as a contraindication However *clinically significant* active rheumatic fever is so unusual in adult life that it should rarely pose a problem in those in whom mitral commissurotomy is indicated The operation is very rarely indicated below the age of 20 Symptoms of heart failure in patients below this age are much more likely to be due to active rheumatic carditis and consequent myocardial dysfunction than to mechanical impediment In the rare patient below the age of 20 in whom disability is regarded as due to the mitral stenosis itself there should be no evidence of rheumatic activity nor history of

rheumatic fever for at least three years The high incidence of Aschoff bodies in left atrial appendages resected at operation (p 817)[64, 179, 81] is not indicative of significant *clinical* rheumatic activity and the surgical results are at least as favorable in patients with as in those without Aschoff bodies in their atrial appendage

Bacterial endocarditis is a contraindication to mitral commissurotomy but the latter may be undertaken six months after the endocarditis has been cured

Other Factors in Relation to Mitral Commissurotomy

Age The usual and preferred age of patients undergoing commissurotomy is between 25 and 50 when cardiac disability usually develops In individuals younger than 25 severe disability usually denotes serious multiple valvular and myocardial disease and/or rheumatic activity but operation may be recommended if pure severe mitral stenosis is believed to be solely responsible for left sided heart failure In one series of 600 patients in whom mitral commissurotomy was performed there were 11 between the ages of 8 and 16[4] In no instance was there a reactivation of rheumatic fever Age beyond 50 and occasionally even beyond 60 is no absolute contraindication but there is increasing probability of myocardial disease as well as valvular stenosis accounting for disability Ellis and Harken[7] reported that 14 patients in Groups II and III between the ages of 50 and 60 and 3 patients in Group IV beyond the age of 60 were operated on without a single mortality but 15 (43%) of 35 patients between the ages of 50 and 60 and classified as Group IV succumbed Janton Glover and O Neill[187] reported successful mitral commissurotomies in 35 patients between the ages of 50 and 60 with only 8 5 per cent mortality

Atrial Fibrillation is not a contraindication and actually most patients undergoing mitral commissurotomy have atrial fibrillation according to some of the reported series of cases

Previous Embolization is not generally regarded as a contraindication although it may indicate increased risk of further embolization during the operation On the other hand repeated embolization which does not cause too serious deterioration of the patient s clinical status is actually regarded as an indication for commissurotomy because excision of the atrial appendage may remove one possible important source of embolization and because improvement in the circulation may diminish the tendency to thrombosis and embolism [6]

Valvular Calcification is no contraindication although it may be responsible for calcium embolization at operation Fracture of a calcified valve may often be accomplished more readily than that of a rubbery fibrotic valve

Pregnancy As a rule mitral commissurotomy should be deferred until after pregnancy *(p 1095) However there have been* occasional reports of successful mitral commissurotomy in patients who became decompensated during pregnancy and were enabled to complete their pregnancy because of the operation [103]

Cardiac Catheterization This procedure is not performed routinely preoperatively but may provide important information which facilitates a decision as to operation in doubtful cases It also provides useful data for evaluating hemodynamic improvement accomplished by the operation The pulmonary artery pressure the cardiac output and the response of both to exercise are objective measurements indicating the presence and severity of mitral stenosis Determination of the gradient across the mitral valve at rest and with exercise gives a more direct appraisal of mitral stenosis The absence of pulmonary hypertension as determined by cardiac catheterization was the basis for rejecting for commissurotomy 11 of 15 patients with mitral stenosis who were regarded as suitable for operation on clinical grounds [84] In some patients with mitral stenosis and unequivocal cardiac disability catheterization studies indicate that the symptoms are due to myocardial insufficiency and not to the mechanical effect of a mitral block [1,3] in these cases mitral commissurotomy was regarded as not likely to prove beneficial However the decision as to operation should not be made on the basis of the catheter findings alone

Preoperative Care

If congestive heart failure is present every effort is made to attain maximal improvement but bed rest should not be prolonged If digitalis was previously administered it is continued if not some surgeons digitalize the patient routinely Sodium intake is restricted activity minimized and

mercurial diuretics are administered as indicated These measures are not instituted if there is no overt evidence of heart failure, except that sodium is at least moderately restricted (1 to 1 5 gm of sodium daily) If the patient was receiving quinidine to control some arrhythmia it is continued but no effort is usually made preoperatively to convert chronic atrial fibrillation to sinus rhythm Sedatives should be administered if necessary to promote sleep at night Reassurance is very important Antibiotics may be started two days preoperatively Occasionally, transfusions are given if there is marked anemia Even if no blood is given preoperatively the patient's blood is grouped and cross matched with blood which is held in readiness if required during the operation Anticoagulants are usually discontinued if they had been administered to prevent thromboembolism, and prothrombin coagulation and bleeding times are checked to be sure that it is safe to operate On the other hand Storm and Hansen[225] found that mitral commissurotomy performed during anticoagulant prophylaxis with Dicumarol on 26 patients was associated with no increase in hemorrhagic phenomena and no case of thromboembolism, whereas these complications occurred as expected in 15 to 20 per cent of patients who did not receive anticoagulants

There is no uniformity about preanesthetic medication Usually a barbiturate is administered the night before operation, and morphine sulfate an hour before anesthesia In addition, Seconal may be given orally or by vein before the patient is taken from his room Bailey and associates[10] administer both Seconal grain 3/4 orally and atropine sulfate grain 1/200 to 1/100 subcutaneously one hour before the anesthetic, but others do not employ atropine procaine or neostigmine The orthopneic patient should be brought to the operating room with his head and shoulders elevated on pillows

Anesthesia

Skillful anesthesia and expert control of respiration with the chest open are of the utmost importance High oxygen intake and very light anesthesia are important features of good anesthesia in these cases Non-explosive anesthetics are used because of the frequent use of the electrocautery However, cyclopropane or ethylene is occasionally used for induction and endotracheal intubation, after which the anesthetist switches to light ether anesthesia Most commonly anesthesia is initiated with nitrous oxide and oxygen by endotracheal tube or by intravenous Pentothal with oxygen administered by endotracheal tube Endotracheal intubation is accomplished after adequate cocainization Because of the open chest, respiration is controlled by external positive pressure to avoid hyperventilation Great care should be taken to avoid anoxia, drug overdosage or excessive positive pressure

Role of the Cardiologist

The cardiologist is constantly in the operating room, observing and interpreting a continuous electrocardiographic tracing on the oscilloscope He must be alert to detect and correct cardiac arrhythmias There is no substantial agreement on the use of drugs to prevent or treat cardiac disturbances during the operation The treatment of cardiac arrest and ventricular fibrillation is discussed on pages 1109 and 377 respectively Atropine 0 5 to 1 0 mg is administered intravenously for severe bradycardia Neostigmine 0 25 mg may be given intravenously and repeated if necessary for paroxysmal (atrial) tachycardia Quinidine and procaine amide (Pronestyl) are not administered prophylactically to avoid myocardial irritability because they cause poor myocardial contractility They are used however, during the operation if necessary to control ventricular ectopic beats or ventricular tachycardia But in the presence of poor myocardial contractility calcium chloride (2 to 4 cc of a 10% solution) or epinephrine (0 2 to 0 5 cc of a 1 1000 solution) is administered

The cardiologist and the anesthetist must be on guard for changes due to hypoxia which may be controlled by an oximeter The cardiologist assists the surgeon in taking pressure measurements directly from the heart during the operation and in supervising the necessary apparatus He must keep the electric defibrillator on hand In addition, a member of the resident staff has the sole function of measuring blood loss and supervising apparatus and materials for infusions or transfusion The cardiologist should determine accurately and record the peripheral arterial pulses preoperatively and postoperatively especially in the presence of atrial fibrillation

The Operation

At the onset of the operation an isotonic

solution of 5 per cent dextrose in water is administered by very slow intravenous drip through a 15 gauge needle or a polyethylene catheter, preferably in two different extremities The use of two needles is recommended[4] to permit rapid transfusion of blood which may become necessary The blood may also be given under pressure For this purpose 2000 to 3000 cc of properly cross matched blood is kept available although only part of this may be used Blood loss is carefully estimated during the course of the operation by measurement of blood removed by suction and by weighing sponges Care must be taken both during the operation and postoperatively to avoid overloading the circulation and causing pulmonary edema

The patient is placed in a right lateral recumbent position[119] A curvilinear incision is made from the sternum anteriorly extending beneath the left breast and posteriorly below and behind the angle of the scapula Or a posterolateral incision is made The fourth intercostal space is opened widely the fourth costal cartilage being divided Sometimes the fifth rib is resected The tip of the pulmonary lingula may be resected for histologic study of the pulmonary vessels The common carotid and innominate arteries may be mobilized and tapes passed around them in order to occlude them temporarily and intermittently to prevent cerebral embolization during each intracardiac maneuver[11] ■ The effectiveness of this procedure has been questioned Despite all preventive measures cerebral emboli have occurred in 5 to 10 per cent of cases but recently preoperative and postoperative anticoagulant therapy was claimed to be effective in preventing thromboembolism[228]

The pericardium is incised posteriorly or anteriorly to the phrenic nerve and the edges held apart by traction sutures A purse-string suture is placed around the base of the atrial appendage and a non crushing Satinsky clamp applied distal to the suture An incision is then made into the apex of the appendage sufficient for the opening to accommodate the index finger snugly If palpation indicates the presence of thrombi the appendage is opened and the first gush of blood is allowed to carry out any free clots or clots are carefully extracted [1] all before the occluding clamp is applied The index finger then enters the left atrium by way of the incision in the appendage while one assistant manages the purse-string suture to prevent bleeding and another controls the tapes around the great vessels If the appendage is very small the commissurotomy may be effected by the small fifth finger If the appendage is too small for this or if it is completely obliterated by thrombus or calcification the finger may enter through an incision in the posterior wall cephalad to the left coronary vessels or through an incision in a left pulmonary vein or through a rubber diverticulum sewed to the myocardium ■

Neptune and Bailey[1] [9] have used a right thoracic (posterolateral or anterior) approach through the right fourth intercostal space when performing an operation for associated lesions such as tricuspid stenosis or interatrial septal defect in combination with mitral stenosis The mitral commissurotomy is carried out through the left atrial wall which is entered near the interatrial groove More recently this technique has been employed on a routine basis for the performance of mitral commissurotomy This is done partly to permit routine exploration of the tricuspid valve because Bailey and Bolton[9] encountered significant tricuspid stenosis in 15 and tricuspid insufficiency in 17 of 98 consecutive patients operated on for mitral stenosis In addition it is claimed that the right-sided approach permits a more effective mitral commissurotomy and avoids the danger of entering through a left atrial appendage which often contains a thrombus The left-sided approach is still recommended for the correction of mitral regurgitation

Simultaneous pressure measurements are taken from the left atrium and left ventricle before the actual commissurotomy and repeated after commissurotomy The difference in pressure in the left ventricle and left atrium in diastole the so-called left atrioventricular gradient is utilized as a criterion of the adequacy of the surgical procedure[138] The preoperative left atrial mean pressure usually between 20 and 40 mm Hg should fall to 10 to 15 mm or less (normal 5 mm) while the gradient of 15 to 35 mm Hg should be reduced to less than 5 mm Hg if possible

With the finger in the left atrium the mitral valve and the subvalvular region are explored The presence of a mitral regurgitant jet and its severity are determined by palpation A small regurgitant jet may be ignored and may in fact diminish if mobility of the cusps is restored Since the anterolateral commissure usually contributes most to the stenosis this is fractured first with the finger exerting gentle pressure toward the annulus sometimes reenforced by counter pressure exerted by the other hand on the outside of the heart A flat guillotine-type knife inserted between gloves on the volar surface of the index finger is often used to incise the commissure if inadequate separation is accomplished by finger fracture but blunt dissection may follow the incision to be certain the commissure is split clear through to the myocardium at the atrioventricular annulus Then the posteromedial commissure is likewise split but this is occasionally omitted if it is very difficult and sufficient enlargement has been attained by splitting the anterolateral commissure In some cases it is the posteromedial commissure which is most responsible for the stenosis and this commissure must then be completely opened by finger fracture or knife Creation of significant regurgitation must be avoided

In addition the finger must be advanced through the valve opening for subvalvular dissection if there is a subvalvular stenosis caused by fusion of chordae tendineae and papillary muscles to each other or to the myocardial wall[10] If the chordae are greatly shortened and finger dissection is ineffective multiple cuts of the commissures are made with a special guillotine knife[192] One may have to cut into the fused mass of papillary muscle

After the stenosis is corrected the finger is withdrawn gently and hemostasis effected by ligating the purse-string suture sometimes by a second ligature

after application of the Satinsky clamp Most of the appendage distal to the ligature is resected and studied histologically The atrial stump may be closed with a single row of closely placed interrupted silk sutures Care must be taken not to occlude the coronary arteries near the base of the appendix as cardiac arrest may result If tapes were placed around the cerebral vessels these are removed The pericardium is thoroughly irrigated with saline and closed loosely with a few stitches A tube is introduced through the seventh intercostal space for underwater closed drainage of the left pleural cavity The ribs are approximated and chest wall then closed in layer

Combined Valvular Lesions

For combined mitral and tricuspid stenosis Harken and Black[119] employ the usual left-sided thoracotomy to perform a mitral valvuloplasty They then explore the right atrium and tricuspid valve through another pericardial incision across the base of the pulmonary artery which exposes the tip of the right atrial appendage Neptune and Bailey[190] use a right thoracic approach and dissect the heart along the interatrial groove The left atrium is entered by incising the septum and a mitral commissurotomy is performed Then tricuspid commissurotomy is effected with the aid of a knife after the finger is introduced by way of the right atrial appendage In the presence of trivalvular stenosis the aortic obstruction is relieved first, then the mitral and finally the tricuspid Among 200 patients operated by Bailey for mitral stenosis from the right side a concomitant aortic commissurotomy was performed in 28 and trivalvular commissurotomy in 4 In 32 (16 per cent) a tricuspid stenosis was found in association with mitral stenosis but without aortic stenosis Of 41 patients operated on for combined mitral and aortic stenosis, 83 per cent were improved 9 per cent were unchanged and 7 per cent worse The over all mortality was 27 per cent but there were no fatalities in the group of 11 patients in whom mitral and aortic stenosis were uncomplicated by other valvular lesions[165]

Postoperative Care

The patient is kept in an oxygen tent for two or three days He is under constant supervision during this period A roentgenogram of the chest is made several hours postoperatively to exclude serious pneumothorax To encourage respiratory excursion of the chest and the elimination of retained secretions the patient is urged to take deep breaths and cough despite his reluctance Intermittent catheter suction, and rarely bronchoscopy, are employed to remove secretions Morphine and similar narcotics are avoided unless absolutely essential But analgesics must be given to relieve pain usually Demerol in small doses at four hour intervals and barbiturates, if essential, to alleviate anxiety and restlessness Fluids are given orally in moderation, but care should be taken to avoid abnormal fluid retention since water is retained, in excess of sodium, during the first three days following mitral surgery[245] Hyponatremia may occur during this period[44] A low sodium diet is maintained postoperatively Diuretics are given if necessary, but this is rare in the immediate postoperative period Digitalis is administered if it had been used preoperatively If antibiotics were not started preoperatively, they are administered postoperatively for about a week or according to the presence of fever or other evidence of possible infection If there is an indication for anticoagulants they may be administered beginning 48 hours after the operation The underwater drainage tube is removed on the day after operation if roentgen ray examination has demonstrated complete reexpansion of the left lung The patient is encouraged to be out of bed at intervals by the third postoperative day and to walk shortly thereafter Patients usually feel better by the fifth or sixth day and fairly well by the tenth Most patients are discharged 10 to 14 days after the operation

Postoperative Complications

The complications for which one must be on the alert include failure of expansion of the left lung acute pulmonary edema or congestive heart failure, pericardial effusion cardiac arrhythmias, pulmonary embolism arterial embolism, psychic depression or frank psychoses and much later the post commissurotomy syndrome[4] Saddle embolism of the aorta is an immediate complication of mitral commissurotomy which must be promptly recognized and corrected[183, 6, 207a]

Paroxysmal atrial fibrillation occurs commonly 24 to 72 hours postoperatively in those with previous sinus rhythm[133] Therefore some physicians administer quinidine prophylactically, 0 3 gm every six hours following the operation When atrial fibrillation occurs the patient should be digitalized speedily with intravenous Cedilanid if the ventricular rate is rapid or digitalis dosage should be increased in those already receiving the drug As a rule

the atrial fibrillation reverts spontaneously to sinus rhythm otherwise quinidine is administered in an effort to restore sinus rhythm if the arrhythmia persists more than a week Heinz and Hultgren[1, 3] found that 34 (45%) of 74 patients with sinus rhythm developed atrial fibrillation postoperatively Reversion to sinus rhythm occurred spontaneously in 30 per cent of these patients usually about the sixth postoperative day, in another 47 per cent conversion was accomplished by quinidine and in 23 per cent quinidine failed

Pulmonary edema should be prevented by avoiding overloading with fluids or sodium If it occurs it should be treated as described on page 292

Arterial embolism may occur in about 6 to 13 per cent of cases[177, 4, 238] Careful palpation of the femoral arteries should be carried out preoperatively and repeatedly postoperatively When indicated (p 582) prompt embolectomy should be carried out[65, 07]

Convalescence

When the patient returns home ordinary activities such as washing dressing and walking are gradually resumed as tolerated but no work or routine duties are undertaken for at least two months Complete improvement and resumption of an essentially normal life may require a year or more In some cases patients must be urged and continually encouraged to increase their activities if they have previously developed an abnormal anxiety regarding the risk of physical exercise On the other hand some patients develop such *euphoria postoperatively* that their enthusiasm must be tempered A low sodium diet is given varying from 200 to 1000 mg sodium daily according to the degree of previous heart failure After six months sodium intake may be gradually liberalized if there are no symptoms or signs of heart failure and if none appear as the sodium allowance is increased Similarly the need for digitalis may be reevaluated after six months to a year In those with persistent heart failure maintenance doses should be continued in those with chronic atrial fibrillation the dose should be sufficient to keep the ventricular rate between 60 and 80 per minute at rest

Post Commissurotomy Syndrome[77, 218, 1374]

After mitral commissurotomy 10 to 63 per cent of patients have been reported to develop a clinical picture which has been termed the post commissurotomy syndrome It is characterized by the sudden onset 10 days to two months after the operation of severe and often disabling pain in and around the area of the incision The pain is occasionally right sided as well as on the left often radiates to the left shoulder and is usually increased by deep inspiration Occasionally cough dyspnea hemoptysis and arthralgias are associated There is definite fever with daily spikes to 102 to 104° F and sweats but no chills Leukocytosis a rapid erythrocyte sedimentation rate and a positive serum C reactive protein are present but serum antistreptolysin is not increased A pleural pericardial rub and/or pleural effusion are common and similarly there may be a pericardial rub or *evidence of pericardial effusion* The attacks usually last one to two weeks occasionally longer and multiple attacks are common Recovery without sequelae is universal Bacteriologic cultures of pleural and pericardial fluid are negative

The etiology is unknown The site and nature of its manifestations suggest that the syndrome is caused in some manner by the local trauma and reaction to the operative procedure Likoff[166] reported a similar febrile illness in six adults following surgical correction of pulmonary stenosis with interatrial septal defect The interval between the operation and onset of symptoms suggests a hypersensitivity reaction to antigens in the operated area There is no consistent evidence of postoperative infection or pulmonary embolism to account for the syndrome The post commissurotomy syndrome has been attributed to a reactivation of rheumatic fever[218] but there is no direct evidence favoring this concept The usual finding that the effusions were blood stained led Papp and Zion[1374] to attribute the syndrome to postoperative oozing from the atrial wound with loculation of the effusion and left basal pulmonary consolidation as possible additional factors

Treatment is unsatisfactory but salicylates may afford relief occasionally and Demerol or opiates may be necessary for the most severe pain All in all prednisone cortisone hydrocortisone and pituitary corticotropin (ACTH) have proved to be most frequently beneficial

Results of Mitral Commissurotomy

The *evaluation of therapeutic results* following mitral commissurotomy is often difficult since it is based largely on subjective reports

of symptoms and capacity for physical work.[217] Patients are often anxious to be cooperative and exaggerate their increase in functional capacity. Many patients who claim to be entirely well are found to be unable to meet ordinary daily requirements of activity.[28] Psychologic factors often promoted by restrictions prescribed by physicians, have led in many patients to self imposed disabilities over a period of years. After the operation the *restrictions are removed and the patient* discovers capacities for activities which may have always been present but never tested. That the operation may be falsely credited with a beneficial result is exemplified by the instances in which striking improvement is reported even though the chest was opened but a mitral commissurotomy was not or could not be performed. But these cases should not be overemphasized because the improvement is temporary. Furthermore, it is highly probable that most instances of clinical improvement are due to relief of the obstruction at the mitral orifice. Conversely, there are occasional instances in which anxiety and other factors associated with the disability caused by the baneful effects of the mitral stenosis cannot be overcome, even though the operation relieves the stenosis. In such cases psychic resistance to increasing activity may *negate an anatomically and physiologically* satisfactory surgical result. Another difficulty in evaluation is raised by the possible role of better medical care and the rest period associated with the preoperative, postoperative and convalescent period, as contrasted with the role of the operation itself in effecting the improved clinical result.

In general, *satisfactory therapeutic results* have been reported in about 65 to 75 per cent of patients operated on for mitral stenosis.[[illegible], 4, 141, 113, 133, 211, 142, 98, 96, 104] About 10 per cent or somewhat less succumb to the operation and about 15 to 25 per cent do not experience substantial benefit. In evaluating reported data it should be remembered that the operation is designed essentially to alleviate a serious mechanical impediment imposed by the stenosed mitral valve. It does not usually restore normal valve function or directly modify persistent rheumatic carditis, myocardial damage or advanced pulmonary changes. A favorable result according to most reports is therefore based on the patient's functional ability to carry out normal activities without discomfort, and his freedom from distressing symptoms, especially attacks of pulmonary edema. It does not include any improvement in physical signs, in roentgen ray or electrocardiographic evidences of cardiac enlargement or hypertrophy or even substantial improvement in certain hemodynamic values.

In a report by L. B. Ellis and Harken[75] of *the clinical results in the first 500 patients* operated by mitral valvuloplasty, the over all mortality was 11.6 per cent, in the last 400 it was 9.3 per cent. However, whereas the mortality rate in Group IV has averaged about 25 per cent, that for patients in Groups II and III has ranged between [illegible] and 7 per cent and more recently is said to approximate 1 per cent.[75, 119] Similarly, F. H. Ellis, Kirklin, et al.[73] reported an operative mortality of 8.4 per cent in 131 patients, ranging from zero in Groups I and II (26 patients) to 4.5 per cent in Group III (67 patients) and 21 per cent of 38 patients in Group IV. Bailey and Bolton[9] reported an over all mortality of 7.7 per cent in 1000 cases of mitral commissurotomy. The mortality rate was 3 per cent for 32 patients in Class I, 3 per cent for 344 patients in Class II, 10 per cent for 562 patients in Class III and 18 per cent for 62 patients in Class IV. *Operative mortalities of 3 to 9 per cent have* been reported in various series by other surgeons.[15, 19, 133, 167, [illegible], 4, 104] In all the series, the mortality rate is much higher among patients classified as Group IV. Advancing age up to 60 had relatively little influence provided patients were in Group II or III. The operative mortality is somewhat higher in *patients with atrial fibrillation* than in those with sinus rhythm, and the incidence of peripheral embolization during operation was much higher in the former group.[177] The finding of significant mitral regurgitation, a discoid mitral valve with rubbery or leathery cusps or deforming plaques of calcium in the cusps, or inadequate surgical opening of the valve, led to poor or imperfect results.

Operative deaths are usually due to hemorrhage, shock, ventricular fibrillation or cardiac standstill, embolization, renal shutdown, tension pneumothorax and congestive heart failure, especially that due to induced severe mitral regurgitation. As technique has improved, embolism, due to migration of clots

from the left atrium or of calcium particles from the mitral valve [redacted] the chief source of morbidity and mortality

Follow up Results

From the viewpoint of relief of symptoms and greater capacity for work 70 to 90 per cent of those patients who survive the operation are reported to be greatly or significantly improved For example of 49 patients classified as Group III preoperatively by the standards of the New York Heart Association 20 were classified as Group II and 20 as Group I after the operation But even the results in the majority of patients in Group IV are very good relative to their previous state of invalidism

In addition to the preoperative clinical status of the patient the anatomic status of the mitral valve is a determining factor in the therapeutic result Immobile valves and rubbery cusps which do not yield readily to dissection by finger or knife are often responsible for failure In about half the cases failure is due to preoperative mitral regurgitation It has not been demonstrated that an unsatisfactory clinical result was due to irreversible preoperative pulmonary vascular narrowing

It is presumed but not proven that the favorable operative results are associated with greater longevity than [redacted] to be expected without operation There are claims that the incidence of peripheral embolization in patients with atrial fibrillation is diminished after the operation but such postoperative emboli have occurred [116]

Physical Signs and Hemodynamic Results There is usually no remarkable change in cardiac murmurs Occasionally the diastolic murmur is fainter or disappears and occasionally a systolic murmur appears [197] The intensity of the first sound is reduced in about half the cases and that of the loud second pulmonic sound is likewise reduced in about one third [197] Preoperative atrial fibrillation persists paroxysmal atrial fibrillation is common postoperatively in those with preoperative sinus rhythm and occasionally persists The cardiac size and configuration are not consistently altered except that the shadow of the left atrial appendage is decreased or absent The cardiac shadow may be temporarily enlarged by postoperative pericardial effusion In a serial study of preoperative and postoperative x ray films of the chest in 20 patients Soloff and Zatuchni [14] observed enlarged cardiac shadows in 11 Their belief that this is due to rheumatic reactivation is not supported by acceptable evidence It is possible that it is due in some cases to strain and enlargement of the left ventricle following relief of the mitral stenosis The electrocardiogram shows no consistent change but may show evidence of the postoperative appearance of left ventricular hypertrophy

Early follow up cardiac catheterization studies of cardiovascular hemodynamics indicated that marked functional improvement occurred without significant change in the pulmonary arterial and right ventricular pressures [183] This may be due to irreversibility of pulmonary vascular lesions or to a longer period necessary for return to normal In some instances however a fall in right ventricular and pulmonary arterial pressure has been noted The resting cardiac output and the increase with exercise have been augmented following operation The left atrial pressure is greatly diminished and the left atrioventricular gradient substantially diminished Judson et al [183] noted that physical improvement after mitral valvulotomy was generally paralleled by an increase [redacted] renal plasma flow glomerular filtration and salt and water excretion during and after exercise Furthermore there was usually a significant elevation of the stroke index a lowering of the pulmonary pressures and a reduction in total pulmonary resistance

It has been repeatedly reported that good or excellent clinical results have been obtained in patients in whom there was little or no improvement in the hemodynamic findings [183 4 241] In particular an elevated pulmonary artery pressure presumably due to irreversible narrowing of the pulmonary arterioles may persist virtually unchanged after [redacted] clinically successful operation However reversibility is possible but may require six months or longer On the other hand improvement in the hemodynamic abnormalities including a reduction in pulmonary artery pressure has been found to accompany a good clinical result in many cases [55 61 71] [redacted]

It is difficult to accept the implication that an operation designed to alleviate clinical symptoms by correcting the mechanical defect and consequent hemodynamic abnormalities which cause those symptoms can be successful clinically without altering the hemodynamic abnormalities When such a lack of

correlation is reported, one may infer that relief of the stenosis was inadequate and that the clinical functional improvement is due either to better medical care relief of anxiety regarding the danger of physical exertion or other psychic factors

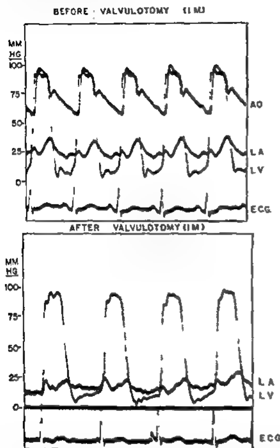


Fig 126 Simultaneous pressure pulses in left atrium left ventricle and aorta in mitral stenosis before and after mitral valvulotomy Note end diastolic pressure in left atrium is 24 in left ventricle is 6 i e there is a gradient of 18 mm Hg Following valvulotomy gradient is 3-5 mm Hg (Courtesy Dr A Gordon)

A successful mitral commissurotomy should permit the admission of two fingers into the mitral orifice, should reduce the left atrial and pulmonary capillary pressure to less than 15 and preferably less than 10 mm Hg should virtually eliminate the atrioventricular gradient[159, 40] or reduce it to less than 5 mm Hg (Fig 126), and significantly reduce the resting pulmonary arterial blood pressure as well as its rise on exercise One would anticipate also an increase in the diminished resting cardiac output with a greater rise in response to exercise but these improvements in blood flow have not been noted, as a rule[84] The improvement in hemodynamics actually obtained is indicated by the data of F H Ellis et al[73] The mean left atrial pressure, which was usually between 22 and 38 mm Hg preoperatively, was reduced to between 15 and 25 mm Hg the pulmonary artery wedge (pulmonary "capillary") pressure from between 20 and 35 to between 10 and 22 mm Hg, the resting mean pulmonary artery pressure from between 35 and 70 to between 15 and 35 mm Hg the pulmonary arteriolar resistance from a range of between 100 and 700+ to between 100 and 320 dynes/sec/cm^{-5} after operation The increase in cardiac output during exercise, which ranged from 0 to 1 liter per minute per square meter had increased several months after operation to between 0 5 and 2 5 liters Wade and associates[37] found the most marked improvement following mitral commissurotomy in the response of the cardiac output and ventilation during exercise

Restenosis of the Mitral Valve Isolated cases have been reported in which the authors have concluded that restenosis of an operated mitral valve has occurred[143, 67, 73, 151] It may be difficult to distinguish by clinical observation whether the valve has actually undergone restenosis or whether the symptoms and signs are due to inadequate commissurotomy of the preoperative mitral stenosis In a review of 42 late postoperative deaths among 600 patients operated on for mitral stenosis over a five-year period Glover et al[10] found no instance in which death could be attributed to the recurrence of mitral stenosis Autopsy studies in 31 cases failed to disclose any true endothelialization of the cut surfaces or evidence of any process which could cause restenosis of the valve

Late postoperative deaths may be due to progressive cardiac failure due to advanced irreversible heart disease, which could not be stemmed by relieving the mechanical hindrance to coexistent unrelieved dysfunction of other valves to aggravation of or induced mitral insufficiency or to failure to perform an adequate commissurotomy or to bacterial endocarditis or non cardiac diseases

Other Surgical Treatment

Other operative procedures previously recommended have been largely abandoned with the development of mitral commissurotomy This applies to the creation of an artificial

atrial septal defect[21] to provide an additional path of egress for the left atrial blood thus relieving pulmonary congestion Resection of the left atrial appendage for recurrent embolism[20] is now generally performed as part of the operation of mitral commissurotomy Resection of the left atrial appendage removes only about 50 per cent of the mural thrombi on the left side of the heart which may be responsible for systemic emboli[144] Inferior vena caval ligation has been performed in very advanced cases of mitral stenosis with right and left heart failure especially with recurrent pulmonary embolism and this procedure has also been used as a preliminary to mitral commissurotomy which is performed 6 to 24 months later[17]

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Chapter 27

AORTIC INSUFFICIENCY (AORTIC REGURGITATION)

ETIOLOGY AND PATHOLOGY

Insufficiency of the aortic valve is due almost exclusively to rheumatic fever or syphilis. Occasionally aortic insufficiency may result from bacterial endocarditis or from trauma. It may be associated with pronounced hypertension[19] and aortic atherosclerosis, or dissecting aneurysm of the aorta (p. 556).[41] Congenital aortic insufficiency may be due to perforation or abnormal placement of the cusps and a congenitally bicuspid valve may result in aortic regurgitation. The relative incidence of rheumatic and syphilitic aortic insufficiency depends chiefly on the varying geographical incidence of rheumatic fever and syphilis. Aortic insufficiency in patients below the age of 35 is almost always rheumatic. Uncomplicated rheumatic aortic insufficiency may occur but it is often combined with mitral valvular disease. Aortic insufficiency occurs predominantly in males in contrast with the predominance of mitral stenosis in females.[3]

Rheumatic Aortic Insufficiency

Rheumatic fever invades the aortic valve by way of the aortic valve rings. The valve becomes thickened by edema, inflammatory cells and granulation tissue. Verrucae develop at the line of closure as a result of the extrusion of degenerated inflamed superficial valvular tissue and the secondary deposition of thrombotic material from the blood stream. The inflammatory exudate becomes organized and scar tissue is formed which subsequently contracts. The cusps become stiff, thickened and deformed. They are shortened and their free margins are thickened, rolled and often inverted toward the sinus pocket. These alterations become more advanced with recurrent attacks of rheumatic fever and secondary degenerative changes including atheroma and calcification.

The valve becomes insufficient because (1) the shortened cusps are too small to close the normal aortic orifice, (2) the deformity and rigidity of the cusps prevents their proper coaptation, (3) the annulus may become compromised by rheumatic changes with consequent loss of tensile strength and dilatation of the aortic ring. Subsequently aortic stenosis may be associated or may become the predominant lesion. Varying degrees of aortic stenosis may be associated with aortic insufficiency. But in the presence of free (wide open) aortic regurgitation severe aortic stenosis is rare.

Syphilitic Aortic Insufficiency

The cardiac and aortic lesion of syphilis will be described in detail (p. 89?). The *aortic valve* is affected by extension of the aortic syphilitic inflammatory tissue to the valve cusps. Unlike the rheumatic lesions, syphilis hardly ever attacks the valve cusps directly but confines its mischief to the aortic valve commissures (syphilitic commissural valvulitis). Aortic insufficiency in syphilis may be due to three factors: (1) widening of the commissures, (2) shortening of the cusps so they cannot reach each other to occlude the orifice, and (3) dilatation of the aortic orifice concomitant with dilatation of the ascending aorta. Since the cusps become separated, not adherent as in rheumatic fever, aortic stenosis does not develop. However, I have, in occasional instances, seen calcific aortic stenosis in hearts with syphilitic aortic insufficiency and similar cases have been reported.

Aortic Insufficiency in Bacterial Endocarditis

Aortic insufficiency in cases of subacute or acute bacterial endocarditis is usually the result of a previous rheumatic inflammation. Frequently, however, the bacterial vegetations erode the valve substance and either produce an aneurysm of the cusp or perforate it. Thus a previously normal valve may become insufficient or a previous insufficiency may be intensified. Furthermore, the valvular vegetations themselves, if large, may prevent perfect apposition of the cusps and closure of

the aortic orifice Non traumatic rupture of an aortic valve is usually due to bacterial endocarditis but may occur with syphilitic aortitis and rarely in rheumatic or atheromatous valves [11] In rupture of the aortic valve due to bacterial endocarditis there is often an abrupt onset or increase in heart failure there may be chest pain and usually there are signs of 'free' aortic regurgitation An aortic diastolic murmur first appears or undergoes a change in character [11, 5]

Traumatic Aortic Insufficiency

Aortic insufficiency results rarely from trauma In 1928 Howard[3] collected from the literature 113 cases of valvular disease due to trauma most of which were unproven The aortic valve is more often injured than any other valve The injury may result from the *strain* of an unusually strenuous muscular effort[11] or from *direct trauma* caused by a blow to the chest wall[40] or a fall from a height Rupture of the aortic valve by contrecoup as a result of a blow to the chest wall was demonstrated experimentally by Barié[3] on cadavers The injury is presumed to occur when the ventricles are in early diastole and the aortic valves under maximum tension Traumatic aortic insufficiency is encountered almost exclusively in males

Pathologic examination usually reveals a linear tear of a valve cusp More than one cusp may be affected Not infrequently the valve injury is part of an extensive tear involving the root of the aorta In instances of muscular strain the cusp is more apt to be torn at its attachment to the aorta, in instances of trauma it is usually torn through its free margin The ruptured valve or aorta is generally the seat of preceding disease especially syphilis or bacterial endocarditis Occasionally a normal valve may be ruptured [35]

Clinically traumatic rupture of the aortic valve may be characterized by chest pain and the rapid development of an aortic diastolic murmur, progressive intractable heart failure and the circulatory signs of free aortic regurgitation Surgical correction of a ruptured aortic valve has been accomplished by Leonard et al [40] by insertion of a plastic aortic valve in the first part of the descending aorta

Atherosclerosis and Hypertension (Functional Aortic Insufficiency)[25, 27]

I have occasionally observed clinical evidence of aortic insufficiency in patients with pronounced atherosclerotic dilatation of the aorta and hypertension, whose aortic valves were normal at postmortem examination Garvin[19] found 14 such cases among 200 consecutive cases of hypertensive heart disease studied at autopsy

Dissecting Aneurysm and Marfan s Syndrome

In occasional cases of dissecting aneurysm of the aorta the dissection may involve the attachment of the aortic cusps, or the aneurysm may interfere with their closure [29] Chronic dissecting aneurysm of the aorta may simulate chronic rheumatic heart disease due to the development of aortic insufficiency [41] In cases of Marfan's syndrome or arachnodactyly (p 728) aortic insufficiency is encountered more frequently than is generally recognized [28] The aortic valvular insufficiency is secondary to medianecrosis of the aorta and dissection

Rheumatoid Arthritis

Occasionally aortic insufficiency appears in adult life in patients with rheumatoid arthritis without a history of rheumatic fever

Congenital Interventricular Septal Defect with Aortic Insufficiency (p 747)

PATHOLOGIC PHYSIOLOGY

Volume and Effects of the Reflux

The dynamic effects of aortic insufficiency are due to a significant regurgitation of blood from the aorta into the left ventricle [53] Allan[1] observed in artificial circulation experiments that large refluxes were obtained with leaks equal to one half to one seventh of the area of the aortic orifice The normal valve area is 3 sq cm Gorlin et al [23] determined that a regurgitant orifice area of no greater than 0 5 sq cm was associated with refluxes of 2 to 5 liters per minute because of the large regurgitation pressure gradient (between aorta and left ventricle) in diastole Wiggers and Maltby[55] determined that the amount of the reflux depended essentially on the size of the leak the larger the leak the larger the reflux In addition to the size of the regurgitant orifice the size of the pressure gradient from the aorta to the left ventricle in diastole and the duration of diastole are important factors determining the amount of regurgitant flow The quantity of reflux may amount to more than 50 per cent of the systolic discharge [55, 43, 23] With large leaks most of the regurgitation occurs in the early part of diastole before the mitral valve is open so that there is little interference with the inflow

of blood from the *left atrium* In *small leaks* most of the regurgitation takes place late in diastole after the opening of the mitral valve But the magnitude of the reflux with small leaks is too slight to affect significantly the entrance of blood from the left atrium Thus neither with small nor large leaks is there a rise in intra atrial pressure

The effective cardiac output is usually normal at rest and as a rule rises with exercise in contrast with that in aortic stenosis[23] Also in contrast with aortic stenosis, left ventricular *pressure and work can be increased in response to exercise* The pulmonary capillary diastolic pressure in aortic regurgitation is normal at rest but rises with exercise Clinical symptoms may be correlated with the degree of this *increase in pressure* *Cardiac* catheterization of the left ventricle by way of the radial artery disclosed normal diastolic pressures in patients with compensated aortic regurgitation and elevated left ventricular diastolic pressures averaging 25 mm Hg in those with heart failure[58]

Cardiac Compensations for the Aortic Reflux

Despite the large reflux a relatively normal cardiac output is maintained by (1) a more forceful contraction of the left ventricle (2) a prolongation of the period of systolic ejection

1 The addition of the aortic reflux to the normal inflow from the left atrium increases the diastolic volume of the left ventricle and its initial intraventricular tension According to Starling s Law of the Heart this results in a more powerful contraction of the left ventricle and a greater ejection of blood in systole

2 In experimental and clinical aortic insufficiency the phase of isometric contraction is shortened while the period of systolic ejection is prolonged to the same degree Thus in addition to the higher pressure attained the left ventricle has a longer period of ejection in which to expel its increased diastolic volume The diminished *aortic diastolic pressure* against which the ventricle ejects its stream is an additional compensatory aid In animal experiments an increased cardiac rate also helps to maintain a normal cardiac output but this factor *does* not usually *operate* in human aortic insufficiency in the absence of heart failure

Effect of Aortic Insufficiency on Cardiac Size

The increased diastolic blood volume and intraventricular tension *in the left ventricle lead to enlargement of that chamber* Rosenbach[50] who first produced aortic insufficiency in rabbits noted an initial dilatation followed by hypertrophy of the left ventricle Other observers have also repeatedly demonstrated cardiac hypertrophy in animals following experimental aortic insufficiency[16, 4, 50]

In human aortic insufficiency dilatation and hypertrophy of the left ventricle are invariably found in cases with significant regurgitation The hearts in human aortic insufficiency are the largest encountered in cardiac pathology They are the so-called ox hearts or cor bovinum of classical literature The weight generally exceeds 500 gm often 750 gm and occasionally even 1000 gm The enlargement involves chiefly the outflow *tract (the anterior half of the left ventricle* and interventricular septum) which becomes greatly elongated and hypertrophied The endocardium in this region is often whitened and thickened and there may be crescentic thickenings or pockets (birds nests) resembling secondary valve structures below the aortic valve The e endocardial changes are mute evidence of the tension of the regurgitant stream

CLINICAL FEATURES

STAGE OF COMPENSATION

Whereas in mitral stenosis *perfect* compensation for a long span of years is the exception in aortic valvular disease it is the rule In mitral disease the *limited compensatory* power of the weak left atrium and the absence of an efficient valve between it and the pulmonary veins permit some degree of pulmonary congestion (and exertional dyspnea) *early in the disease* In *aortic valvular* disease the strong left ventricle and the efficient mitral valve may long prevent any stasis in the pulmonary circuit

In the absence of complications patients *with pure or predominant aortic insufficiency* often live many years or even a normal life span either without knowledge of their disease or without significant disturbance I have known a number of such individuals who engaged *actively in strenuous sports or in* occupations involving hard physical labor

Occasionally even with almost perfect compensation there are subjective disturbances due either to local cardiac compensations or to *the peripheral changes in vascular dynamics*

The enlarged heart with its forceful precordial heave may be very discomforting to the patient especially on lying down Lying on the left side must usually be avoided He may be greatly disturbed by the audible beat of his heart and cervical vessels as he rests against the pillow There is sometimes an uncomfortable ticking in the throat due to vascular pulsation of the uvula Sleep may be disturbed by these sensations or by terrifying dreams The latter usually occur when there is some degree of cardiac failure Generally the patient, if compensated becomes adjusted to the various pulsations and his sleep is little if at all disturbed *Dizziness,* particularly with sudden change of position, is not rare and is probably due to transient cerebral anemia caused by rapid severe changes in pressure in the cerebral vessels

Certain symptoms encountered in aortic insufficiency are not due to the valvular disease itself but to associated lesions When due to rheumatic heart disease aortic insufficiency is usually combined with mitral disease and not infrequently with aortic stenosis These may modify the clinical picture When aortic insufficiency is due to syphilis luetic narrowing of the coronary arteries is generally associated and aortic aneurysm may occur In patients beyond middle age with either rheumatic or syphilitic aortic insufficiency, there is frequently an associated atherosclerosis of the coronary arteries *Paroxysmal dyspnea* which Longcope[44] emphasized as a frequent manifestation of luetic aortic insufficiency is generally due to left ventricular failure and is not a symptom of the compensated stage *Cardiac pain,* also described as a typical feature of luetic aortic insufficiency is usually not due to the valvular lesion as such Its occurrence is of sufficient interest to merit special discussion

CARDIAC PAIN IN AORTIC INSUFFICIENCY

Angina pectoris has long been regarded as a symptom of aortic insufficiency, but it is rarely due to the uncomplicated valvular lesion itself In the cases of syphilitic origin *the cardiac pain is usually due to the frequently* associated stenosis of the coronary ostia and not infrequently to concomitant coronary atherosclerosis Angina pectoris is very uncommon in uncomplicated rheumatic aortic insufficiency but in older persons it may occur because of coronary atherosclerosis or because superimposed calcification of the aortic valve leads to stenosis It occurs rather frequently in patients with free aortic regurgitation and congestive heart failure

Schwartz,[51] and later Lewis,[42] reported a distinct form of angina pectoris in cases of rheumatic aortic insufficiency, occurring in severe paroxysms, usually at night The attacks were accompanied by a rise in blood pressure, increased pulse and respiratory rate palpitations and by vasomotor disturbances such as flushing and sweating The pain occurred at rest but sometimes was precipitated by excitement It was often relieved by nitroglycerin But I have seen one patient with this syndrome who had such severe and persistent pain that he took 25 or more tablets of nitroglycerin *(each 1/100 grain) daily to obtain* relief

Cardiac pain in uncomplicated (rheumatic) aortic insufficiency has been attributed to (1) diminished coronary flow because of a low diastolic pressure and (2) increased demand for blood because of the increased weight and work of the hypertrophied heart But this explanation does not completely explain all the facts Thus it is not clear why so many patients with rheumatic aortic insufficiency and an extremely low diastolic pressure fail to have angina pectoris Laplace[37] denied the significance of the low diastolic pressure in the production of cardiac pain in aortic insufficiency because this symptom was less frequent in a group of patients with extremely low diastolic pressure than in the group with moderately low diastolic pressure Finally it is uncertain whether the coronary blood flow is actually diminished in aortic insufficiency despite the low diastolic pressure Thus Green [7] found that the minute coronary flow was increased because the improved flow during systole more than compensated for the reduction during diastole By catheterizing the coronary sinus in patients with aortic insufficiency Bing et al [7] found the coronary blood flow and cardiac oxygen consumption increased

LEFT VENTRICULAR FAILURE IN AORTIC INSUFFICIENCY

Failure of the left ventricle in aortic insufficiency usually occurs after a relatively long period of perfect or nearly perfect compensation The left heart failure of aortic insufficiency differs in some respects from that of

mitral stenosis because in the former it is the left ventricle in the latter the left atrium that gives way Because of the greater strength of the left ventricle as compared with that of the left atrium a longer period elapses before left heart failure occurs in aortic insufficiency than in mitral stenosis

In rheumatic aortic insufficiency increasing fatigue of the greatly enlarged heart associated degenerative disease of the coronary arteries intercurrent infections and other factors may contribute to the development of heart failure In the syphilitic variety stenosis of the coronary ostia is an important contributory factor Left ventricular failure is associated with dilatation of that chamber and of the mitral orifice with consequent functional mitral insufficiency The dilatation of the left atrium which follows is inadequate to compensate effectively for the regurgitation due to the sudden failure of the left ventricle and mitral incompetence

Dyspnea on exertion is the earliest signal of left heart failure in aortic insufficiency as it is also of mitral stenosis This is slight at first but becomes rapidly and progressively worse Long periods of dyspnea on exertion without other symptoms of failure may occur occasionally but usually other severer symptoms are soon associated An outstanding and characteristic symptom of left heart failure in aortic insufficiency is a most distressing form of *paroxysmal dyspnea* It appears in sudden attacks lasting up to fifteen minutes sometimes after exertion but much more often while the patient is at rest especially while asleep Paroxysmal dyspnea is especially characteristic of luetic aortic disease as depicted in Longcope s vivid description [44] It also occurs with rheumatic aortic insufficiency but is much less common than with the syphilitic type The difference in incidence may be due on the one hand to the frequent narrowing of the coronary ostia in syphilitic disease and on the other to the modifying effect of associated mitral defects in rheumatic aortic insufficiency

Orthopnea sooner or later is added to the above-mentioned symptoms

In some patients with very severe aortic insufficiency with diastolic pressures below 50 mm Hg and with the hemodynamics of free aortic regurgitation gallop rhythm and left heart failure an atypical form of *angina pectoris* occurs commonly The pain is often worse in recumbency and during the night intensified in certain positions and only transiently or incompletely relieved by nitroglycerin Attacks of myocardial infarction are frequently suspected Recurrent and sometimes intractable epigastric or diffuse abdominal pain occurs commonly and various x ray studies are made repeatedly without disclosing an organic basis for the pain Deficient blood flow to the abdominal viscera analogous to the coronary insufficiency of aortic regurgitation and resembling that due to atherosclerotic narrowing in Ortner s syndrome is suspected Pounding of the heart distressing throbbing and tenderness of the carotid arteries excessive sweating and heat intolerance are additional manifestations Sudden death is frequent in this group of patients

In cases of aortic insufficiency due neither to rheumatic fever nor syphilis symptoms of left heart failure may be absent or overshadowed by other features of the causative disease In *subacute bacterial endocarditis* the valvular lesion may be indicated only by a change in character of the aortic murmur or by the fresh development of an aortic diastolic murmur In *atherosclerotic* aortic insufficiency there may be no clinical evidences of the lesion except the murmur In the uncommon cases of *traumatic aortic* insufficiency the lesion may be denoted by the murmur alone without associated symptoms but is characterized usually by anginal pain rapid development of progressive heart failure or by shock and a rapid demise

RIGHT SIDED HEART FAILURE IN AORTIC INSUFFICIENCY

The symptoms of left sided heart failure in aortic insufficiency are eventually combined with or overshadowed by those of failure of the right ventricle The agony of severe paroxysmal dyspnea is sometimes relieved when the right heart fails and diminishes the forward pressure and engorgement in the lungs The right ventricle dilates the tricuspid valve becomes insufficient and the right atrium is enlarged by reflux and stasis The venous pressure in the venae cavae and peripheral veins rises As a result the neck veins and those on the extremities appear engorged the liver becomes enlarged palpable and tender and peripheral edema is

observed Ascites may be somewhat less common than in mitral stenosis but hydrothorax is frequent

OBJECTIVE EVIDENCES OF AORTIC INSUFFICIENCY

Cardiac Signs

Inspection and Palpation The apical impulse is heaving and located to the left of and below its normal site Occasionally it is seen or felt far out in the left axilla or as low as the sixth or seventh interspace Sometimes there is a diffuse systolic *depression* of the anterior chest wall medial to the forceful apical thrust This depression is caused by the aspirating effect of the contracting ventricle on the chest wall as its large volume of blood is expelled into the arterial tree[14] A diastolic pulsation of the chest wall is due to the filling of the left ventricle

Percussion may disclose the enlargement of the left ventricle but this is best demonstrated by roentgenologic examination

Auscultation The characteristic sign is a soft, high pitched *diastolic murmur* likened to the sound made by the pouring of water In luetic aortic insufficiency it is often louder and lower pitched than in the rheumatic form of the disease In cases of traumatic etiology, the murmur is often extremely loud and musical in quality[8] or it may resemble the cooing of a dove[9] or the call of the sea gull (sea gull murmur)[10] In cases due to extreme physical exertion the murmur may be audible without applying the stethoscope or the ear to the chest

Interest in the sea gull murmur of aortic insufficiency has increased in recent years Most frequently it is heard in syphilitic aortic insufficiency but occasionally also in aortic insufficiency due to bacterial endocarditis to rheumatic fever or to rupture of the valve[20] This musical murmur has come to be regarded as a specific murmur usually due to eversion or retroversion of the right anterior aortic cusp[■ 82] The musical quality is related phonocardiographically to the regularity of its vibrations which are composed virtually of a pure sine wave in the oscilloscope[23] Musical or sea gull murmurs are not always aortic diastolic Loud musical murmurs in cases of ruptured mitral chordae calcification of the mitral valve or calcific aortic stenosis may be sea gull in character and systolic in time

The diastolic murmur starts immediately after the second sound Occasionally the second aortic sound is absent The murmur is best heard in the second right intercostal space or along the left border of the sternum in the third or fourth interspace Occasionally the murmur has been described as being loudest in the pulmonic area, and rarely near the apex or left axilla In my experience, the diastolic murmur of rheumatic aortic insufficiency is usually best heard along the left border of the sternum, while that due to luetic disease is best heard either in this location or in the second right interspace

The high pitch and soft quality of the diastolic murmur of aortic insufficiency make it one of the most difficult to hear, and one about whose presence in a given case there is most disagreement This applies particularly to the rheumatic form of aortic insufficiency, whereas the diastolic murmur of syphilitic aortic regurgitation is readily audible Thrills are rarely associated because of the high frequency of the murmur The murmur may often be more readily discovered with the naked ear or a straight, wooden monaural stethoscope I have heard the murmur most readily with the Bowles type of stethoscope Recognition is enhanced if the patient is examined while standing or sitting and bending slightly forward Elevating the arms and holding the breath in expiration also help

A *systolic* murmur over the base of the heart often accompanies the diastolic murmur of uncomplicated aortic insufficiency It may be high pitched and blowing or harsh and loud The combined systolic and diastolic aortic murmurs produce the characteristic "bellows murmur" In Corrigan's[12] original description of aortic insufficiency, the aortic systolic blowing murmur and its propagation into the carotid and subclavian arteries were described as characteristic of the disease In my experience, this systolic murmur usually occurs in the luetic cases, and is present in rheumatic aortic insufficiency when there is considerable stenosis The systolic murmur is probably due to concomitant dilatation and changes in the wall of the adjacent aorta it may therefore represent a functional (relative) aortic valvular stenosis

An *apical systolic murmur*, independent of that in the aortic region, may also be present when the left ventricle fails becomes dilated and produces a relative mitral insufficiency

The second pulmonic sound may then become accentuated due to increased pressure in the pulmonary circulation

The Austin Flint Murmur in Aortic Insufficiency

Occasionally there is a low rumbling late diastolic or presystolic apical murmur in aortic insufficiency which is indistinguishable from the characteristic murmur of mitral stenosis This murmur in a case of aortic insufficiency without organic mitral stenosis has been termed the Austin Flint murmur after the man who first described it [18] It may be associated with a diastolic thrill My experience conforms with the observation of Laubry and Pezzi[43] that the Austin Flint murmur is generally heard when there is left ventricular failure The frequency of the murmur has been variously estimated but in routine clinical practice it is encountered only occasionally

The explanation of the Austin Flint murmur is still disputed [18] The aortic regurgitant stream may force the anterior (aortic) mitral leaflet (which is nearest the aortic valve) upward thus producing a functional mitral stenosis impeding the inflow of blood from the left atrium This explanation is supported by the clinical and experimental observations of Herrmann[30] who found that the Austin Flint murmur occurred when the posterior aortic cusp was incompetent This is the leaflet nearest the anterior mitral cusp and the one whose insufficiency would most readily permit a regurgitant stream to strike the anterior mitral cusp Gouley [4] found evidence of a defect in the right aortic cusp The murmur occurs most frequently if left ventricular failure ensues With digitalization or relief of failure by other therapeutic methods the Austin Flint murmur may disappear This disappearance after relief of failure confirms the interpretation that the murmur was of the Austin Flint type According to the phonocardiographic observations of Luisada[45] the so-called Austin Flint murmur is usually either a gallop rhythm due to an audible atrial sound or an auditory misinterpretation of the heart sounds i e a first sound which is crescendo or split In rheumatic aortic insufficiency the diagnosis of an Austin Flint murmur is hazardous because of a frequently associated mitral stenosis which is more likely to produce a presystolic murmur The clicking third sound and palpable tap of organic mitral stenosis do not accompany the Austin Flint murmur and when present may help as distinguishing signs

Roentgenologic Examination of the Heart

1 With perfect compensation and slight or early lesions the cardiac outline may appear relatively normal since a small degree of left ventricular enlargement is indistinguishable With more advanced lesions the heart assumes a characteristic *aortic configuration*



Fig 127 Rheumatic aortic insufficiency Woman aged 38 Prominent ascending aorta Enlarged elongated left lower contour of hypertrophied left ventricle

(Figs 127 and 40 p 103) The lower left cardiac contour which in the anteroposterior view represents the left ventricle becomes elongated and enlarged downward and to the left The angle formed with the pulmonary artery salient is much sharper than normal The figure of the resulting heart shadow has been described as boot-shaped the rounded apex of the heart corresponding to the toe of the boot The aortic knob is usually prominent and the rest of the aortic shadow may be slightly dilated The pulsations of both the left ventricle and the aorta have an increased excursion as observed on fluoroscopic examination or on roentgenkymograms In the left oblique (second) position with the left shoulder rotated anteriorly toward the screen the large left ventricle is seen encroaching on or even extending behind the shadow of the spine (Fig 40*B* p 103)

2 *With left ventricular failure* there is a functional insufficiency of the mitral valve with secondary dilatation of the left atrium and of the pulmonary vessels The cardiac shadow now assumes some of the features of mitral disease which modify the aortic configuration ("mitralized aortic configuration") The modification is more striking if mitral stenosis is associated with aortic insufficiency

3 *When right heart failure develops* both the right ventricle and right atrium become dilated The total cardiac shadow appears huge with an extremely wide transverse diameter

The Electrocardiogram in Aortic Insufficiency

In well developed cases there is usually a pronounced left axis deviation The major deflections are of high voltage There may be a depression in ST_1 and an inversion of T_1 as well as corresponding changes in the precordial leads denoting left ventricular hypertrophy (p 111) (Fig 46 p 109) The R waves in the left precordial leads are of strikingly high voltage When aortic insufficiency is associated with mitral disease variable pictures are obtained Often there are tall broad or notched P waves as well as left ventricular preponderance

Peripheral Signs of Aortic Insufficiency

In many cases with small leaks there are slight or no significant alterations in blood pressure and pulse pressure and no striking peripheral vascular phenomena In cases with large leaks described as "free aortic regurgitation"[4] distinctive peripheral signs of aortic insufficiency listed below may be noted "Free aortic regurgitation" may occur in aortic regurgitation of any etiology but is observed most commonly with syphilitic aortic regurgitation and in that due to rupture of an aortic cusp

1 Low Diastolic and High Pulse Pressure A low diastolic pressure is characteristic of aortic insufficiency The pressure as indicated by the change in sound over the brachial artery to a muffled tone is usually 50 mm Hg or lower Often the sounds continue to be heard until the pressure in the blood pressure cuff is zero Since the systolic pressure is usually normal or somewhat elevated the difference between it and the low diastolic pressure gives a pulse pressure which is usually increased Instead of a normal of 30 to 50 mm Hg the pulse pressure usually exceeds 80 mm and often reaches 100 mm or more In a young man of 30 with syphilitic aortic insufficiency, I observed a blood pressure of 300/38 i e a pulse pressure of 262 mm Hg The diminished diastolic pressure is the result of aortic regurgitation with consequent relative diastolic emptiness and relaxation of the arterial tree

2 Corrigan (Radial) Pulse Aortic insufficiency is often associated with a characteristic pulse (*Corrigan pulse*[1]) which strikes the palpating finger with a rapid forceful jerk and quickly disappears (celer et alter) It is described as having a *waterhammer* quality because of its sudden impact, and a *collapsing* quality because it falls away so rapidly The waterhammer impression is the consequence of the sharp rise in aortic pressure and the rapid filling of the radial artery The collapse which begins toward the end of systole, is due to the sharp fall of pressure in both the central and peripheral arteries It has also been explained as the result of the very increased velocity head of the blood stream and the consequently rapid egress of blood from the arterial system[**] The waterhammer effect is accentuated if the pulse is examined by grasping the wrist with the examiner's whole hand with the patient's arm elevated because the radial artery is then in more direct line with the outflow stream from the aorta and because gravity increases the blood pressure changes at the wrist The waterhammer shock is also audible as a pistol shot sound if the examiner listens with his stethoscope over the radial artery[47] While the Corrigan pulse is characteristic of aortic insufficiency it may occur in cases of patent ductus arteriosus arteriovenous fistula Graves disease and in severe anemia, fever and conditions associated with peripheral vasodilatation

The *pulse wave* as seen on sphygmograms shows a sharp almost vertical tall upward limb and a steep downward stroke

The *pulse rate* is normal in well compensated cases In failure a moderate tachycardia (90 to 100 per minute) is frequent

3 Visible Arterial Pulsations. Sometimes a tentative diagnosis of aortic insufficiency can be ventured on observing marked pulsations in the neck vessels Such visible pulsations result from the sudden systolic filling of the large collapsed arteries Corrigan's[1] graphic description of aortic insufficiency contains a vivid picture of these visible pulsations in

both carotid arteries in the temporal arteries and in other large vessels The forcefulness of these pulsations may impart a to and fro motion to the entire head synchronous with the cardiac cycles (de Musset s sign) With the ophthalmoscope one may also observe pulsation of the retinal arteries as well as of the veins F Müller[48] described pulsations in the uvula Rosenbach[50] in the liver and Gerhardt[21] in an enlarged spleen

4 Capillary Pulsation Quincke[43] observed an alternate paling and flushing of the skin in aortic insufficiency which he ascribed to capillary pulsation (Quincke pulse) Clinically this phenomenon may be elicited in several ways (a) by observing the nail bed or skin at the root of the nail while pressure is made on the tip of the nail (b) by observing the edge of the blanched region when the mucous membrane of the lip is compressed by a glass slide, (c) by observing the earlobe or fingertip while it is being transilluminated by a flashlight Actually the phenomenon observed is due not to the pulsation of the capillaries but to that of the subpapillary arteriolar and venous plexuses which are essentially responsible for the redness of normal skin Lewis and Drury[13] attributed capillary *pulse to arteriolar dilatation but this explanation does not appear to apply to the ' capillary pulse of aortic insufficiency The capillary pulse is not pathognomonic of aortic insufficiency It may also be observed in a normal subject when the skin is warm in a number of unrelated conditions such as fever anemia Graves disease and whenever there is local dilatation of the terminal peripheral vessels*

5 *Disproportionate Femoral Systolic Hypertension (Hill s Sign)* Hill and Rowlands[21] observed that the slight physiologic excess of blood pressure in the femoral artery over that in the brachial was greatly exaggerated in aortic insufficiency Instead of the normal difference in systolic pressure amounting to 10 to 20 mm Hg in aortic insufficiency this difference may be 60 to 100 mm Hg or more Since the femoral artery is in a direct line with the aortic stream while the brachial issues from the aorta at a right angle the femoral artery receives not only the pressure head but also the velocity head of the aortic stream In normal persons the velocity head is slight and the femoral pressure exceeds the brachial by a correspondingly small amount But since in aortic insufficiency the velocity head is considerable there is a pronounced excess of pressure on the femoral as compared with the brachial artery Hill s sign is absent in cases of functional aortic insufficiency associated with hypertension

6 *Pistol shot Femorals Femoral Double Tone (Traube s Sign) Femoral Murmur (Duroziez s Sign)* Auscultation over the femoral artery reveals a booming sound synchronous with each pulse through the vessel This characteristic sound has been described as resembling a pistol shot and is probably due to vibrations of high frequency caused by the sudden elevation of pressure in the vessel [9, 34]

Sometimes a double sound (*Traube s double tone*[44]) is heard in aortic insufficiency instead of the single pistol shot ' Its mechanism is uncertain

A systolic murmur is heard over the femoral artery in normal individuals if the vessel is slightly compressed by the bell of the stethoscope This murmur is due to the vibrations set up by the rapid passage of blood past an obstruction In aortic insufficiency a diastolic as well as systolic murmur is audible over the compressed vessel because there is a rapid diastolic regurgitation toward the heart as well as systolic forward passage toward the periphery This characteristic double murmur is termed *Duroziez s sign*[15] Like capillary pulsation it is not a pathognomonic sign and is observed in other conditions with a rapid peripheral blood flow or vascular dilatation, such as Graves disease febrile states anemia and on warming the lower extremity

COMPLICATIONS

Cardiac failure is the most frequent complication of aortic insufficiency It is almost an integral part of the course of the disease because there are few or no significant symptoms before failure develops *Subacute bacterial endocarditis* frequently complicates aortic insufficiency usually while the lesion is still well compensated When the complication occurs the underlying aortic insufficiency is almost always rheumatic In luetic aortic insufficiency *narrowing of the coronary ostia* is generally associated This produces an *anginal syndrome* cardiac failure and often sudden death Bronchial and pulmonary infections and embolization may complicate aortic insufficiency but rarely in comparison with their occurrence in mitral stenosis Atrial

fibrillation and other arrhythmias are relatively uncommon

DIAGNOSIS

The diagnostic features of aortic insufficiency are (1) a *high pitched diastolic murmur* over the aortic area or along the left border of the sternum or occasionally in the cardiac apical region, (2) *enlargement of the left ventricle* especially as indicated by the characteristic boot shaped cardiac shadow seen roentgenologically, (3) *distinctive peripheral circulatory phenomena* such as the high pulse pressure and low diastolic pressure, the collapsing (Corrigan) pulse, visible arterial pulsations capillary pulse femoral pistol shot and Duroziez s sign

The characteristic diastolic murmur is in itself sufficient to justify the diagnosis, on the other hand a diagnosis of aortic insufficiency should rarely be made in the absence of the murmur even when the other clinical features are present Sometimes the roentgenologic findings of left ventricular enlargement and pronounced aortic pulsations, or the peripheral circulatory findings, first suggest the diagnosis, but the latter is proved by the subsequent discovery of the diastolic murmur

The diastolic murmur of aortic insufficiency may have to be distinguished from the Graham Steell murmur of pulmonic insufficiency The latter should be diagnosed only in the presence of mitral stenosis or pulmonary disease sufficient to produce significant right ventricular hypertrophy The peripheral phenomena of aortic insufficiency do not accompany the Graham Steell murmur, the cardiac shadow shows right not left ventricular enlargement and the aorta is not prominent and conspicuously pulsatile The electrocardiogram shows evidence of left ventricular hypertrophy when the diastolic murmur is due to aortic insufficiency of right ventricular hypertrophy when the murmur is due to pulmonary insufficiency

The *etiologic diagnosis* usually involves distinction between rheumatic and syphilitic aortic insufficiency The history of rheumatic fever or syphilis the knowledge of the duration of the murmur and serologic study may be helpful The association of mitral stenosis suggests that the aortic insufficiency is rheumatic The presence of a loud aortic systolic murmur and a diastolic murmur which is most audible in the second right interspace usually denote a syphilitic etiology for the aortic insufficiency A very soft high pitched diastolic murmur along the left border of the sternum is usually of rheumatic origin

Traumatic insufficiency is suggested by a history of unusual physical exertion or penetrating or nonpenetrating injury to the chest followed by a loud, musical murmur (sea gull murmur)

Aortic insufficiency may be attributed to a bacterial endocarditis if an aortic diastolic murmur first appears during the course of the disease Frequently this denotes a preexistent bicuspid aortic valve [8]

PROGNOSIS

The prognosis and treatment are discussed in detail in the chapters on rheumatic fever, syphilis bacterial endocarditis and congestive heart failure

In general the prognosis in cases of *syphilitic aortic insufficiency* is much less favorable than in the rheumatic cases Sudden death is common in the syphilitic cases due to associated coronary ostial involvement Sometimes specific antiluetic therapy relieves the chest pain, it probably prolongs life (p 902) Adequate early treatment of uncomplicated syphilis is more important, for it prevents the occurrence of the cardiovalvular complication

In the *rheumatic cases* the outlook is favorable once rheumatic fever becomes inactive Satisfactory treatment of bacterial endocarditis has greatly reduced the hazard from this complication

SURGICAL TREATMENT OF AORTIC INSUFFICIENCY

Various operative techniques have been employed for the correction of experimentally produced aortic insufficiency, but no method has been generally acceptable when applied to the human lesion Hufnagel and associates[33, 34] placed a rigid prosthetic plastic ball valve in the descending aorta thus preventing regurgitation of blood into the left ventricle The plastic valve is a one-piece barrel shaped tube composed of (1) an inlet (2) a chamber containing a polyethylene ball which opens and closes the valve and (3) an outlet The valve functions in any position and may be opened or closed by a differential pressure of 5 mm Hg The prosthesis is placed in the descending arch of the aorta just beyond the

left subclavian artery where it is capable of controlling about 75 per cent of the regurgitant flow The actual insertion of the valve requires 3 to 6 minutes whereas the aorta at this operative site may be safely occluded up to a maximum of 20 minutes The valve is not placed in the ascending aorta because of the danger of impairing the coronary blood flow and because it would be necessary to interrupt the venous flow to the heart To insure proper fit of the prosthesis in the aorta a small cuff of Orlon mesh is utilized and to prevent angulation a segment of the aorta is removed By these improvements in technique peripheral embolization has been eliminated

Hufnagel and associates[33, 34] operated on more than 100 patients with aortic insufficiency of varied etiology, but chiefly rheumatic In the first 80 cases 50 per cent of the patients had severe refractory heart failure and were virtually terminal patients All the patients had free wide-open aortic insufficiency with heart failure and most of them had angina pectoris There was an over all hospital mortality of 20 per cent Another 20 per cent died in the following two years Essentially all of the others were able to carry out a relatively normal routine after the operation Anemia and sudden death have occurred within the first postoperative week The functioning of the valve produces a noise to which the patient adjusts himself Other people do not hear the noise unless the patient stands with his mouth open and allows the sound to be conducted up the main stem bronchus

Following operation the pulse contours in the lower extremities became normal while those in the upper extremity (proximal to the plastic valve) remained Corrigan in type The absolute volume of regurgitation was diminished and the cardiac output increased[45] The cardiac murmurs diminished in intensity At first the sound of the opening and closing of the valve is audible with the stethoscope or even the unaided ear but it gradually diminishes after weeks or months as the valve becomes covered with fibrous tissue There was a marked increase in exercise tolerance and the need for mercurial diuretics was abolished or their frequency of administration diminished

If aortic stenosis is combined with insufficiency the aortic prosthesis may be inserted first and the aortic valvulotomy performed thereafter The possibility of performing a mitral commissurotomy and inserting an aortic valve may also be considered when mitral stenosis and aortic insufficiency are both significant lesions

Bailey[2] designed a prosthesis consisting of a ball of Nylon mesh suspended by two tails By a transaortic approach with partial exclusion of the aorta and the use of a pericardial pouch as a poncho the Nylon ball is properly placed in the aorta at the valve level and the proper position and mobility maintained by securely suturing its two tails brought through silicone discs The Nylon ball moves with the blood stream in systole and falls back to occlude the aortic orifice in diastole When aortic insufficiency is due to dilatation of the aortic annulus (ring) the defect is corrected by constricting the ring by a tapered Nylon sash sutured in position Among the last 18 patients operated on by these techniques Bailey and Likoff[2] reported three operative and two late deaths but most of the survivors showed marked benefit

ARTERIOVENOUS FISTULA

Arteriovenous fistula[66, 77, 88] denotes a direct communication between an artery and vein often with the formation of an aneurysmal sac This subject is included in this volume because the lesion imposes a strain on the heart and may induce heart failure Because its circulatory dynamics are somewhat similar to those of aortic insufficiency, they are discussed in this chapter There are also many similarities to patency of the ductus arteriosus which may be viewed as a form of congenital arteriovenous fistula

ETIOLOGY AND PATHOLOGY

Arteriovenous fistula may be acquired or congenital The commonest cause is *trauma* A stab gunshot or shrapnel wound often appearing small externally perforates an artery and vein which are in close proximity and often in the same sheath The femoral or

iliac vessels in the thigh and the carotid artery and internal jugular vein in the neck[46] are most often affected Rupture of a syphilitic aortic aneurysm into the superior vena cava, pulmonary artery, right atrium or ventricle produces many of the features of an arteriovenous fistula Surgical cure of traumatic arteriovenous aneurysm between the aortic arch and left innominate vein has been reported [76, 78]

The involved artery becomes dilated for a long distance proximal to the fistula and its wall becomes thinned Rarely it may become so atrophied that an aneurysm forms and may rupture The vein becomes dilated locally due to increased pressure Its wall may become as thick as that of an artery A local aneurysmal sac often forms and may pulsate Varicose veins may appear locally A collateral circulation gradually develops to supply the area distal to the fistula

PATHOLOGIC PHYSIOLOGY

The circulatory disturbances[64] are due to a shunt of 20 to 50 per cent of the cardiac output from a large artery to a large vein

The *cardiac output* is usually increased, owing both to an enhanced stroke output and accelerated heart rate [illegible], [79] The tachycardia has been attributed to a Bainbridge reflex due to an increased venous return or to an increased right atrial pressure But the right atrial pressure may be normal The increased rate is stimulated reflexly by the fall in blood pressure caused by the fistula (Marey s reflex) and is mediated by the vagus nerve

When heart failure develops, the cardiac output falls somewhat but still remains higher than normal Exercise is associated with an increase in cardiac output in compensated patients, with no increase or a reduction in output in patients with congestive heart failure [57]

The *blood volume* is usually augmented [68, 81] especially with the development of heart failure In experimental arteriovenous fistula only the plasma volume is expanded [63] The *circulation time* is diminished because of the short circuit of blood The combination of accelerated speed of circulation and enlarged blood volume is responsible for an increased venous return which is translated into an augmented cardiac output

The *systemic venous pressure* is normal in the absence of heart failure But Cohen and associates[67] observed a moderate increase in right atrial pressure as determined by intracardiac catheterization

Arterial blood pressure (see below)

Closure of the fistula diminishes the cardiac rate, the cardiac output and the blood volume and elevates the blood pressure by eliminating the region of diminished resistance [74] The mean right atrial pressure the diastolic pressure in the right ventricle and the mean pulmonary arterial pressure were found to decrease in some hearts but remained unchanged in others [64]

CLINICAL FEATURES

The diagnostic feature is a machinery like *continuous bruit* or murmur with slight systolic accentuation, heard over the site of the fistula [illegible] It is usually accompanied by a *thrill*

At the site of the fistula there may be a pulsating aneurysmal mass The superficial veins are often dilated and tortuous The affected vein proximal to the fistula has an elevated pressure and an abnormally high content of oxygen due to the arterial shunt [illegible] Chronic venous insufficiency due to venous hypertension may lead to varices, stasis pigmentation and ulceration

There may be ischemia of the part distal to the fistula and occasionally gangrene results Eventually the development of a collateral circulation and the elevated cardiac output provide more than the normal blood flow Consequently the affected extremity may have a higher skin temperature than the normal one and may grow longer if the fistula develops before growth is completed

The Blood Pressure A high pulse pressure is present due to a significant fall in the diastolic pressure with little or no change in the systolic The waterhammer pulse and other peripheral circulatory phenomena observed in cases of aortic insufficiency may also occur with arteriovenous fistula

The *pulse rate* is usually increased But especially characteristic is the slowing of this rate (bradycardiac reaction) on compression or excision of the fistula the so called Branham s sign [57] Following atropinization this slowing does not occur [79]

Cardiac enlargement is usual With small fistulae it may be demonstrable only by comparison of the size of the heart before and

after excision[73] The extent of cardiac enlargement varies with increasing size of the fistula with the size of the feeding artery with the duration of the fistula and perhaps to a slight degree with the proximity to the heart

Cardiac enlargement is dependent on the increased venous return and consequently on the increased stroke output of the heart With increasing venous return there is an increased diastolic volume and increased diastolic tension which result in dilatation and hypertrophy (Chapter 4) It is improbable[71] that a diminished coronary blood flow accounts for cardiac enlargement as Lewis and Drury[7] suggested The reversibility of cardiac enlargement following cure of the fistula has suggested that most of the enlargement is due to dilatation However it is probable that there is a significant degree of hypertrophy and that this is also reversible[III]

Cardiac failure eventually develops in long standing cases of large arteriovenous fistula In several such cases which I observed it appeared probable that coronary insufficiency due to atherosclerosis contributed to the failure of a heart enlarged by an arteriovenous fistula

Complications These include congestive heart failure ulceration or gangrene of an extremity and rarely bacterial endarteritis[69] or aneurysm or rupture of the proximal part of the artery supplying the fistula

Congenital Arteriovenous Fistula

This arises from embryonic communications between arteries and veins which fail to close[75] The extremities intracranial vessels and the face and neck may be affected In recent years congenital arteriovenous aneurysm of the lung has aroused special interest (p 792) Hemangiomata of the liver may provide multiple arteriovenous fistulae which produce right ventricular hypertrophy and right heart failure in infancy[88] The communications in congenital arteriovenous fistulas are more often multiple and more extensive than in the acquired cases Varicose veins ulceration increased growth of an extremity are also more frequent in the former Increased sweating and growth of hair near the fistula occur frequently Congenital hemangiomata are often associated On the other hand bruits are less common and the bradycardiac response less pronounced in the congenital cases

Congenital Pulmonary Arteriovenous Fistula (see p 792)

DIAGNOSIS

The diagnosis of arteriovenous fistula depends on the finding of the characteristic bruit over the fistula It is confirmed if the bruit disappears and the heart slows on compression of the artery proximal to the fistula Arteriovenous fistula should be sought whenever unilateral veins or signs of venous insufficiency are found following an injury or when one limb is warmer or longer than the other Arteriography may be helpful in diagnosis[III]

TREATMENT

Treatment of acquired arteriovenous fistula is essential to avoid cardiac strain and failure as well as the other complications listed Even when frank heart failure is present correction of the fistula usually causes a dramatic restoration of normal circulation as well as a reduction in cardiac enlargement It is important to permit sufficient time to elapse for the development of an adequate collateral circulation before operation and to preserve this collateral circulation at operation[44] Otherwise there is risk of gangrene or other evidence of acute or chronic ischemia Sympathectomy before or during operation diminishes this complication[80] Formerly quadruple ligation of the artery and vein and simultaneous excision of the aneurysm were usually performed[45] This obliterated a main artery It appears probable that more satisfactory results with less subsequent arterial insufficiency of an extremity can be obtained by a transvenous arteriorrhaphy in which the arterial leak is repaired while the vein is ligated[47] If the blood volume is very high it may be desirable to perform a venesection at the time of operation to avoid flooding of the heart when the fistula is closed

Treatment of congenital arteriovenous aneurysms is much more difficult because they are usually multiple and more extensive The treatment of arteriovenous aneurysm of the lung is discussed elsewhere (p 793) Congenital arteriovenous fistulas in the lower extremities may be treated conservatively by compression of the varices with pure rubber bandages

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Chapter 28

AORTIC STENOSIS

ETIOLOGY AND PATHOLOGY

Aortic stenosis has long been considered an *uncommon* valvular lesion. In recent years, however, a number of clinical, roentgenologic and pathologic reports have emphasized the relative frequency of this lesion and led to its recognition during life as well as post mortem.[... 40, 1, 6] Clawson and his co-workers[16] reported 200 cases of calcified aortic valve out of 490 healed valvular deformities. More than 70 per cent of these 200 cases showed severe aortic stenosis. According to these figures this is the commonest lesion of the aortic valve. Aortic stenosis of varying degree is often combined with mitral stenosis and aortic insufficiency, lesions whose clinical and pathologic features frequently overshadow or obscure those of aortic stenosis. Thus in Cabot's[11] series of 148 cases of predominant aortic insufficiency, 93 also had aortic stenosis, and in the series of McGinn and White[49] of 159 cases of mitral stenosis 50 revealed a simultaneous aortic stenosis. Conversely, Bailey et al.[4] found that 44 per cent of their patients with aortic stenosis had significant mitral stenosis. Furthermore, tricuspid valvular disease was present in 17 per cent of the patients with rheumatic mitral and aortic valvular disease.

Non-calcific Aortic Stenosis

The *calcific* and *non-calcific* forms of aortic stenosis may be distinguished with respect to etiology and pathology. Non-calcific aortic stenosis is almost exclusively due to rheumatic fever and is usually associated with mitral stenosis and aortic insufficiency. It is encountered chiefly in patients below the age of 50; males predominate only slightly.

The rheumatic inflammatory exudate produces thickening and deformity of the aortic valve.[34] It leads to agglutination of adjacent cusps by filling the commissures between them. Adhesion usually begins at the less mobile portion of the cusps at their aortic insertion. With organization and scar formation the valve cusps become thickened, firm and more or less fixed in position. The fixity of these *rigid cusps* and their adhesion to each other leads to the formation of a solid ring of fused leaflets which greatly narrow the circumference of the aortic orifice. There may be only a minute triangular aperture in the center of the aortic ring. The degree of narrowing is variable, but significant dynamic effects and clinical symptoms are produced only when the normal circumference, which averages 7.5 cm., is reduced to 2 cm. or less or the *area* of the aortic orifice is reduced from the normal 3 sq. cm. to 0.5 sq. cm. or less. Gorlin et al.[?] estimated that the critical orifice area below which significant dynamic disturbances occur was 0.5 sq. cm. in cases of pure aortic stenosis and 1.5 sq. cm. in cases of aortic stenosis and insufficiency. As the cusps become completely fused and rigid, the aortic orifice is kept open in diastole and systole and there is some degree of insufficiency.

Occasionally there is a greater degree of fusion of the left and right (anterior) cusps than of the others, resulting in a virtual bicuspid valve resembling the congenital bicuspid valve. Thus there may be considerably more mobility in the posterior cusp than in the anterior cusps. Secondary calcification is more pronounced in the anterior cusps. The aortic aperture is displaced posteriorly.

Calcific Aortic Stenosis

Calcific aortic stenosis is distinguished from the non-calcific form by its remarkable clinical symptoms, its predominant occurrence in males (two to five times as often as females) and the relatively advanced age of death.[26, 33, 40, 6] It is agreed that *rheumatic fever* causes almost all of the cases of calcific aortic stenosis[15] but some are undoubtedly of non-rheumatic etiology.[15, 28, 43]

The *congenital origin* of some cases of calcific aortic stenosis has been claimed.[12] Boas and associates, on the basis of studies of

serum cholesterol level suggested that calcific aortic stenosis may be favored by or due exclusively to hypercholesterolemia.[9] Barr et al[5] reported a case of familial hypercholesterolemia in a boy who died at the age of 20 from the complications of extensive atherosclerosis and in whom there was extreme calcific aortic stenosis. There were lipophages deposits of cholesterol crystals and other evidence of atherosclerosis or xanthomatosis in the calcified valve but no stigmas of rheumatic fever in any part of the heart.

Monckeberg[31] separated a primary sclerocalcific form of aortic stenosis from that due to rheumatic fever on the basis of histologic differences (*Monckeberg's ascending sclerosis, sclerosis annularis valvularum*). These differences have been confirmed by the pathologic studies of Sohval and Gross.[35] The following are the essential pathologic distinctions: (1) In the rheumatic cases lipid and calcium secondarily infiltrate the preexisting rheumatic inflammatory lesions and scars. In the nonrheumatic cases sclerotic, lipoidal and calcific deposits are primary. (2) In the nonrheumatic valves calcification begins and is most extensive in the sinus pocket and base of the valve from where it progresses gradually to the free border. In rheumatic valves, the calcification begins and is most extensive in the distal third of the valve. (3) In the nonrheumatic valves the calcific process affects primarily the fibrous layer of the valve cusp on the aortic surface of the leaflet. Calcification in rheumatic aortic valves occurs predominantly in the spongiosa and ventricularis layers on the ventricular aspect of the aortic cusp. (4) Rheumatic calcific aortic stenosis is frequently associated with rheumatic disease of the other valves, especially mitral stenosis; the nonrheumatic form is much more apt to be an isolated valvular lesion. In advanced cases the valve cusps, ring and commissures are entirely converted into a nodular stony mass and an etiologic diagnosis may be difficult or impossible.

The calcific sclerosis may involve structures adjacent to the aortic cusps and sinus pocket. The calcific process may extend by way of the intervalvular fibrosa, like the extension of a luetic aortitis, to implicate the anterior mitral cusp or the bundle of His in the interventricular septum.[6] The coronary ostia and arteries are often remarkably free of atherosclerosis but I have observed cases with myocardial infarction or fibrosis due to recent or old atherosclerotic coronary occlusions. More frequently there are diffuse patchy areas of fibrosis or necrosis without coronary narrowing or occlusion and probably due to coronary insufficiency caused by the valvular lesion itself.[26] [illegible] Horan and Barnes[37] observed some degree of coronary atherosclerosis in all of their cases of calcareous aortic stenosis, but the amount of sclerosis was inversely proportional to the degree of valvular stenosis.

Congenital aortic stenosis and *subaortic stenosis* are being recognized with increased frequency.[47] (For discussion, see p. 787.) Congenital aortic valvular stenosis is often associated with a bicuspid aortic valve. Degenerative changes and calcification occur secondarily. In purely valvular stenosis the fused cusps present a dome-shaped or megaphone-shaped diaphragm with a small central aperture. Subaortic stenosis is somewhat analogous to pulmonic infundibular stenosis; in the former the left ventricular outflow tract is narrowed by musculo-fibrous tissue just below the aortic valve. Congenital aortic stenosis is usually associated with poststenotic dilatation of the ascending aorta.

An aortic stenosis has been produced by a mural thrombus of the left ventricle, secondary to myocardial infarction encroaching on the outflow tract.[14]

Acute bacterial endocarditis may produce a functional aortic stenosis by blocking the orifice with large vegetation. I have never seen healing of bacterial valvulitis result in stenosis. Syphilis per se does not produce an aortic stenosis. In 296 cases of aortic valvular disease studied by Campbell and Shackle[25] 50 were due to syphilis but all of these showed aortic insufficiency without stenosis. However, I have seen several cases in which a calcific aortic stenosis was apparently superimposed on or associated with a luetic aortic insufficiency and similar cases have been reported.[7] In these cases one may occasionally see the characteristic syphilitic widening of one of the aortic commissures while the others are obliterated by calcific masses which fuse adjacent leaflets.

The heart in aortic stenosis is usually considerably hypertrophied, and often weighs between 500 and 700 gm. The heart weight tends to increase in proportion to the degree of the stenosis.[6] The heart weight may be considerably less than 500 gm. when the stenosis is

slight or moderate and especially if death occurs from some intercurrent cause before the development of cardiac failure In some cases of asymptomatic aortic stenosis accidentally discovered post mortem I have seen normal heart weights

In the relatively smaller hearts the hypertrophy is entirely confined to the left ventricle In the larger hearts especially those weighing more than 500 gm there is a considerable degree of visible dilatation as well as hypertrophy *When failure is present* the dilatation and hypertrophy involve the right as well as the left ventricle and often also the atria

PATHOLOGIC PHYSIOLOGY

Degree of Obstruction and Circulatory Disturbance

With slight aortic stenosis there may be no disturbances in circulatory dynamics even when the lesion produces a loud systolic murmur In experimental models and animals the aortic orifice must be reduced to approximately one quarter of its normal size to diminish significantly the cardiac output or alter pressure relationships[3] Such extreme lesions are common in human aortic stenosis especially those associated with calcification The effect of a severe experimental lesion is to increase the resistance to the outflow of blood from the left ventricle and cause incomplete emptying of that chamber[44] and this occurs also in human aortic stenosis But *as a rule this disturbance is compensated for* many years Some degree of aortic insufficiency is often associated with aortic stenosis but when the stenosis is very severe the valvular opening is too minute to permit *a significant degree of regurgitation*

During the stage of compensation measurements at operation have shown that the left ventricular systolic pressure is elevated whereas the diastolic pressure is normal (10 *mm* Hg or less) *With left ventricular failure* the diastolic pressure is also elevated More indicative of the degree of aortic stenosis is the gradient between left ventricular and aortic pressures Thus a normal aortic pressure of 120/76 may be *associated* with a left ventricular pressure of 220/30 indicating a gradient in systole of 100 mm Hg Normally the gradient is only a few mm Hg with moderate aortic stenosis 20 to 50 mm Hg and *severe stenosis* 50 to 100 *mm* Hg *or* more[31, 14a, 41a]

Direct measurement of the left ventricular pressure by way of the bronchoscope and a needle in the left atrium[7] similarly shows a left ventricular systolic pressure significantly higher than the pressure in the right brachial artery By means of transthoracic left heart catheterization not only can the degree of aortic stenosis be appraised by measuring the left ventricular aortic systolic gradient but also an associated aortic insufficiency can be detected and the relative severity of each determined[40]

The pulmonary capillary pressure is usually normal but rises with exercise[3] The pulmonary arterial pressure is normal but may be elevated owing to left ventricular failure coexisting *mitral stenosis* or pulmonary vascular changes[30]

The resting cardiac output is usually within normal limits and may rise with exercise but frequently less than normally[31] In cases of severe stenosis the cardiac output is diminished and more significantly it cannot be increased with exercise[32] The limited cardiac output is due to the severity of the stenosis but may be due also to coexisting mitral disease or left heart failure

Compensations in Aortic Stenosis

The residual blood in the left ventricle due to its incomplete emptying is augmented by the normal inflow from the left atrium The diastolic volume and pressure in the left ventricle rise Compensation is effected in two ways

1 The increased diastolic volume and intraventricular pressure cause a more forceful systolic contraction with restoration of normal stroke output (Starling s Law of the *Heart)*

2 There is a slight increase in the period of isometric contraction and a considerable prolongation of the ejection phase and of total systole Thus the diminished output due to *the obstruction is restored to normal in part* by a more forceful systolic ejection and in part by prolongation of the period during which ejection occurs

In humans these temporary mechanisms are eventually *supported by the development* of left ventricular hypertrophy Because clinical aortic stenosis is a lesion which develops very gradually and over a period of many years there is adequate opportunity for the *production of considerable hypertrophy* while the amount of dilatation remains rela

tively insignificant When the stenosis is superimposed on a pronounced insufficiency or when cardiac failure supervenes, there may may be extensive dilatation as well as hyper trophy

CLINICAL FEATURES

Compensated Aortic Stenosis

Compensated aortic stenosis is often asymptomatic being discovered as an accidental postmortem finding Only 6 of the 42 patients in the series studied by Margolis and his co workers[46] complained of symptoms referable to the circulation However in many cases especially late in the course of the disease and when the valvular obstruction is extreme a number of characteristic symptoms may develop even when compensation appears adequate[80] These symptoms, including dizziness, syncope or cardiac pain, may occur prior or subsequent to the development of cardiac failure

In a series of patients with severe aortic stenosis who were subjected to aortic commissurotomy fatigue was the earliest and most frequent symptom dyspnea on exertion was the second and angina pectoris the third most common[44] Vertigo occurred in 48 per cent and syncope in 42 per cent of patients with pure aortic stenosis and less frequently in those with aortic stenosis and insufficiency Atrial fibrillation did not occur in any patient with pure aortic stenosis in this series Peripheral edema hemoptysis and pulmonary edema were relatively infrequent[4]

Angina Pectoris in Aortic Stenosis

Cardiac pain has been noted in 10 to 20 per cent of proven cases of aortic stenosis Angina pectoris occurs more frequently in aortic stenosis than in other valvular lesions Its occurrence in luetic aortic insufficiency is generally due not to the valvular lesion as such but to the syphilitic narrowing of the coronary ostia (p 894)

The cardiac pain is usually a typical angina pectoris of effort, located over the sternum or precordium and radiating to the left arm Boas[5] reported several cases in which the cardiac pain resembled the excruciating persistent variety seen in coronary thrombosis I have personally observed 3 cases in which death occurred with the clinical and electrocardiographic picture of acute myocardial infarction

The pathogenesis of the cardiac pain is still uncertain, a number of possible explanations having been offered (1) Because of the frequent presence of a diastolic murmur in calcific aortic stenosis the cardiac pain has been ascribed to an associated aortic insufficiency This explanation is unlikely because despite the diastolic murmur there is rarely a dynamically significant insufficiency Nor is angina pectoris frequent in uncomplicated aortic insufficiency Furthermore, I have observed angina pectoris in cases of aortic stenosis in which there was no diastolic murmur nor any other clinical evidence of a possible aortic insufficiency (2) Boas[5] believed that the pain was caused by myocardial ischemia due to the obstruction at the aortic orifice But there is no clear explanation as to the mechanism of this ischemia since a normal aortic pressure is often maintained despite the stenosis (3) Contratto and Levine[1] ascribed the angina pectoris to a relative myocardial ischemia caused by the increased velocity of blood flowing past the coronary orifices This was said to result in a tendency to withdraw blood from the coronary vessels by suction This is hypothetical

My own studies support the concept of myocardial anoxia as the basis of cardiac pain in aortic stenosis The pathogenesis of this anoxia varies in different cases (1) Despite the fact that the coronary arteries in aortic stenosis are usually surprisingly smooth not infrequently there is severe *coronary atherosclerosis with narrowing of the lumina* and occasionally there is an atherosclerotic coronary occlusion Bergeron and associates[3] reported that severe coronary atherosclerosis with or without occlusion was found at necropsy in 13 or 17 cases of aortic stenosis in which a clinical diagnosis of angina pectoris had been made Thus angina pectoris in some cases of aortic stenosis is due to the same cause as in cases without valvular disease namely *coronary narrowing with consequent myocardial anoxia* This may be exacerbated by occasional narrowing of the coronary ostia by calcific deposits in the sinus pockets (2) Acute *coronary thrombosis* which may occur as a result of coronary artery disease accounts for most of the cases in which there is an attack of prolonged, excruciating cardiac pain (3) Myocardial ischemia may result from *functional coronary insufficiency* with or with

out associated coronary artery narrowing[26] This merits special discussion

Coronary Insufficiency and Myocardial Necrosis in Aortic Stenosis

The existence of coronary insufficiency in aortic stenosis is supported by clinical pathologic physiologic and electrocardiographic observations The occurrence of angina pectoris in cases with relatively normal coronary vessels has been noted it suggests that there is a physiologic inadequacy in coronary flow despite the absence of mechanical obstruction We have found pathologic support for this concept in a number of cases of aortic stenosis carefully studied at autopsy In several of these cases in which the most detailed search failed to reveal an acute coronary occlusion I have encountered acute myocardial damage varying in extent from focal areas of necrosis to extensive myomalacia[58, 2] In the more severe cases the clinical picture and electrocardiographic changes were those of acute myocardial infarction These are examples of intense functional coronary insufficiency But it is reasonable to assume that similar less intensive myocardial ischemia may account for the cases of angina pectoris without anatomic change either in the myocardium or the coronary vessels

Physiologic support for coronary insufficiency in aortic stenosis is found in the experiments of Green[31] He demonstrated that there was a significant reduction in the minute flow through the coronary arteries and that this flow could not easily be increased when the myocardial demand for blood was increased Even with extreme aortic stenosis an essentially normal aortic pressure is often maintained by an increased left ventricular contraction associated with a tremendous elevation of intraventricular pressure But the latter diminishes the systolic flow (and minute flow) of blood through the coronary arteries by producing an increased peripheral coronary resistance during systole Thus there may be an inadequate coronary flow even at rest This deficiency is greatly increased by exertion since the left ventricle finds it difficult or impossible to augment further the force of its contraction and the aortic pressure

Conduction Disturbances in Aortic Stenosis

Complete heart block bundle branch block intraventricular conduction defects and delayed atrioventricular conduction occur with sufficient frequency in calcific aortic stenosis to be considered features of the disease

The cause of the conduction defects especially of complete heart block has been found in organic disease of the bundle of His owing to an extension of the calcific process from the aortic valve to the fibrous septum[60] While I as well as others have observed such calcific obstruction of the bundle I have also seen various grades of heart block in cases in which such organic changes could not be demonstrated There are additional reasons for believing that the conduction disturbances are not invariably or even usually due to organic interference with conduction by calcium deposits The type and grade of conduction disturbance in a given case vary from time to time Thus in one case of calcific aortic stenosis which I observed the electrocardiogram first revealed only a left axis deviation and a negative T wave in lead I A week later the P R interval was prolonged to 0 28 second shortly afterward there was a transient complete heart block and eventually an intraventricular conduction disturbance In one case in Boas[8] series heart block was likewise transient and occurred only on exertion Angina pectoris developed simultaneously It is difficult to correlate these observations with a fixed organic lesion (lime) in the bundle or its main branches On the other hand they are compatible with the belief that the disturbances in conduction like the cardiac pain are due to myocardial ischemia caused by functional coronary insufficiency In a variable number of cases conduction disturbances are due to associated coronary atherosclerosis The calcification in the septum may be an underlying or predisposing factor

Dizziness and Syncope in Aortic Stenosis

On careful questioning one can often elicit a history of dizziness or faintness especially with exertion or change of position Not infrequently there are more severe attacks associated with syncope which may last for fifteen to thirty minutes McGinn and White[48] noted this symptom in 31 out of 98 clinical cases and Hammarsten[35] in 16 of 63 patients with aortic stenosis Gallavardin[28] and his students have stressed the frequency of syncope of effort in aortic stenosis It is often related to the occurrence of angina pectoris Occasionally there are petit mal seizures or hemiparesis[40]

Several explanations have been offered for the occurrence of dizziness and syncope in this disease (1) Marvin and Sullivan[48] suggested that syncope is due to a hyperactive carotid sinus reflex Contratto and Levine[17] were able to confirm the presence of a hypersensitive carotid sinus in some cases of aortic stenosis with syncope but not in others (2) Gallavardin[28] believed the syncope to be due to a sudden transient cerebral anemia caused by an insufficient aortic output This theory was based on an electrocardiographic observation, made during syncope of effort, that the heart did not stop contracting while the pulse beat disappeared an observation confirmed by Hammarsten[35] But no explanation is presented as to why the aortic output suddenly became inadequate (3) A third explanation, which we have suggested [illegible] attempts to clarify not only the cause of the syncope, but also its occurrence during effort and in individuals who suffer from angina pectoris Both syncope and angina pectoris occur in those individuals in whom the degree of aortic narrowing and consequently the compensatory left ventricular hypertrophy are extreme With usual activity, a normal aortic and consequently a normal cerebral arterial circulation is maintained in these individuals by a tremendously elevated left intraventricular pressure But so little reserve is left for further elevation of this pressure that it cannot be augmented adequately or with sufficient speed when exertion increases the body's requirements for blood Thus with effort, dizziness and syncope result from the cerebral anemia due to cerebral arterial insufficiency As we have seen above (p 701), similar events in these individuals lead to coronary insufficiency and angina pectoris, especially with effort But syncopal attacks may occur in such patients without anginal symptoms

The above explanation does not preclude the occurrence of syncope as a result of a hyperactive carotid sinus reflex in some cases In still others, syncope may be one of the manifestations of an Adams-Stokes syndrome due to the complete heart block occasionally present in aortic stenosis

Sudden Death in Aortic Stenosis

The frequency of sudden death in calcific aortic stenosis has been repeatedly noted but its pathogenesis remains obscure Of 76 patients followed by Willius,[61] 8 had died suddenly Reports of sudden death are also found in 5 to 15 per cent of the cases of McGinn and White,[49] Contratto and Levine,[17] Margolis and his co-workers[46] and of Bergeron et al[4] Marvin and Sullivan[48] gave a detailed account of 9 cases of sudden death in calcific aortic stenosis Sudden death often occurs in individuals who have previously suffered from dizziness, syncope or angina pectoris, and its occurrence may be an extreme expression of the same factors which produce the latter symptoms Sudden death may occur in patients with aortic stenosis with or without cardiac failure

There are probably multiple causes of sudden death in aortic stenosis

(1) The commonest cause of sudden death in general is coronary artery occlusion As we have mentioned, although the coronary arteries are usually fairly normal in aortic stenosis, occasionally there is a typical acute coronary artery thrombus with myocardial infarction

(2) In other cases of aortic stenosis with open coronary vessels, myocardial infarction is occasionally seen as a result of extreme coronary insufficiency This may also account for sudden death In still other cases, similar severe myocardial ischemia may cause death so rapidly that there is insufficient time for the development of an infarct

(3) Severe myocardial ischemia may produce a high degree of heart block which may be associated with cerebral anemia cardiac standstill or ventricular fibrillation These are all theoretical causes of sudden death

(4) Cerebral anemia which in some patients produces dizziness or syncope, may, if extreme result in sudden death

(5) A hypersensitive carotid sinus may produce cardiac standstill and sudden death In some patients this outcome may be the result of a combination of factors Thus reflexes from a hypersensitive carotid sinus may more readily cause sudden death if there is already some degree of myocardial ischemia and conduction disturbance

(6) Two cases have been reported in which sudden death may have resulted from the formation of an occluding thrombus over the stenotic valvular orifice[48] In one case it was suggested death was due to occlusion of the aortic orifice when one cusp became locked under a shelf formed by the other two[19]

Left Sided Heart Failure in Aortic Stenosis

Symptoms of left ventricular failure are

often the first subjective manifestations of the disease *Dyspnea on exertion* may be the earliest and most frequent symptom but usually fatigability is as ociated This may be present for a year or two but often for many years before other symptoms develop The dyspnea often becomes much more intense a few weeks or months before the end Attacks of *nocturnal paroxysmal dyspnea* (cardiac asthma) are infrequent except in the presence of associated mitral stenosis While they usually develop much later in the course of the disease than exertional dyspnea I have seen two patients in whom uch nocturnal at tacks were present for months before there was any respiratory disturbance during the day In both of the e patients there was an as sociated free' aortic insufficiency *Insomnia and nightmares* with or without associated cardiac asthma occasionally occur when there is early heart failure Cough and expectora tion are not infrequent and rarely there is hemoptysis *Orthopnea* is a late and frequent manifestation occurring when the exertional dyspnea is quite severe

Right Sided Heart Failure in Aortic Stenosis

As in aortic insufficiency severe failure of the left ventricle leads to pulmonary con gestion, elevated pulmonary arterial pressure and strain on the right ventricle Failure of that chamber follows shortly but occa ionally only after years of left-sided heart failure In the patients I have observed the symptoms of left sided heart failure did not sub ide when evidences of systemic venous engorgement de veloped as a result of right sided heart failure Peripheral edema appears when dyspnea and orthopnea are severe The course of the dis ease thereafter is rapidly progressive The liver becomes huge reaching to the level of the umbilicus The cervical veins are distended and may pulsate The venous pressure is ele vated Cyanosis appears toward the very end of the disease Effusions in the serous cavities are not uncommon particularly hydrothorax Frequently weakness lo s of weight and emaciation are prominent near the termina tion

OBJECTIVE FINDINGS IN AORTIC STENOSIS

The Heart

Inspection and *percussion* are usually of little assistance especially in elderly persons in whom a rigid barrel shaped chest obscures the pulsations of the heart In younger per sons, one may occasionally note a slow lifting pulsation of the hypertrophied heart

Palpation is important as it may supply a leading clue to the diagnosis There is frequently a *systolic thrill* at the base of the heart to the right of the sternum or along the right cervical vessels Its frequency in verified ca es has undoubtedly been understated because this sign is not always specifically sought when the diagnosis of aortic stenosis is unsuspected Occasionally it can only be elicited if the patient sits or stands and bends forward

Auscultation reveals a long-drawn loud and usually rough rasping squeaking or musical high pitched systolic murmur over the aortic area and the cervical vessels The murmur may radiate not only to the neck, but down ward along the sternum toward the apex and occasionally to the back Occasionally the systolic murmur is most prominent at the apex of the heart An apical systolic murmur may represent a radiation from the aortic area or a complicating relative mitral insuf ficiency when left ventricular failure occurs

The *phonocardiograph* shows the vibrations of a high pitched murmur which may be ex clusively systolic [38] (see also congenital aortic stenosis p 787) Occasionally the phonocardiogram shows the murmur to have a characteristic diamond shaped configuration Leatham[42] and others[43] stress the observation that the systolic murmur of aortic stenosis at the apex as well as the aortic area reaches its peak in mid-systole and is completed before the second sound This contrasts with the systolic murmur of mitral regurgitation which is evenly distributed throughout systole or is late systolic in time and differs from the systolic murmur of pulmonic stenosis which usually extends up to the second sound

The *second sound* over the aortic area is characteristically faint or absent Its absence indicates extreme fixation of the aortic cusp and is associated with the most severe cases of aortic stenosis In milder forms of aortic stenosis there may be no alteration in the second aortic sound Occasionally a normal second sound in the second right intercostal space actually represents a normal second pulmonic sound Auscultation over the first right intercostal space may disclose whether the second aortic sound is actually ab ent, diminished or normal [1]

A *diastolic murmur* over the base of the heart is heard in almost half the ca es of

"pure" monovalvular aortic stenosis It is sometimes accompanied by the peripheral circulatory signs of aortic insufficiency

Pulse and Blood Pressure

The pulse in severe aortic stenosis is often characteristic It is of small amplitude, rises slowly and falls away slowly (pulsus parvus et tardus) Its slow, prolonged elevation (systolic ejection being prolonged in aortic stenosis) gives it the form of a plateau There is an actual delay in the arrival of the pulse at the radial artery as compared with that of the normal pulse In aortic stenosis, the interval between the apex beat and the radial pulse is 0 2 second instead of the normal interval of 0 07 to 0 1 second

Pulse tracings from the radial artery often show a slight anacrotic notch on the ascending limb Hence the pulse of aortic stenosis has sometimes been described as an *anacrotic pulse* The greater the stenosis the lower is the position of this notch When rarely, the notch is quite sharp a double peak is formed and the wave is described as pulsus bisferiens Vibrations at the height of the carotid pulse have been termed carotid shudder [21] Feil and Katz have shown that the anacrotic notch in aortic stenosis is not present in the central arteries e g, in the subclavian Its appearance in the radial artery is merely the peripheral wave manifestation of the sudden change in pressure (recoil) in the aorta when the narrowed aortic orifice offers marked resistance to flow after the first rapid ventricular ejection of blood [0] However Wright[61a] described a similarity in contour of the simultaneously recorded central and radial artery pulses

The *blood pressure* in uncomplicated cases is normal Sometimes, however, the systolic pressure is slightly diminished, and the diastolic is normal or slightly elevated, with a resultant small pulse pressure There is often a prominent auscultatory gap In various series, both the average systolic pressure and the average pulse pressure are elevated because of an associated free aortic insufficiency or essential hypertension in many of the cases Contratto and Levine[17] found 17 cases of hypertension in their series of 180 The average blood pressure was 145/84 the range being between 260/156 and 80/10 In one case of calcific aortic stenosis combined with syphilitic aortic insufficiency, I observed a blood pressure of 300/40

Roentgenologic Examination of the Heart in Aortic Stenosis

In uncomplicated, well compensated aortic stenosis, the cardiac silhouette may appear normal even when there is slight hypertrophy There is usually hypertrophy of the outflow tract of the left ventricle with relatively little dilatation In anteroposterior views, this is indicated by a blunt rounding of the lower left cardiac contour (Fig 39A p 102) By fluoroscopy or roentgenkymography, one may observe a slow ventricular thrust or a gradual prolonged systolic contraction When left heart failure develops, the heart may become "mitralized" as in aortic insufficiency (p 690) When right-sided heart failure also develops, the cardiac shadow shows universal enlargement to the left and right

The aortic shadow in "pure" aortic stenosis, in contrast with that of aortic insufficiency is either normal or diminished in size and pulsation

Roentgenologic examination of the heart has assumed special importance in the diagnosis of the calcific type of aortic stenosis Fleischner [4] first diagnosed calcification in the annulus fibrosus during life, and subsequently Sosman and Wosika,[47] and other have reported series of verified cases in which antemortem diagnoses of calcified mitral and aortic valves were made by roentgenologic examination The calcification can be demonstrated fluoroscopically and on overpenetrated films In fluoroscopy, it is important to be extremely well accommodated, and to use a beam of high penetration coming through a very small aperture in the screen The calcified deposits should be localized by rotating the patient so as to determine the best views Recent studies indicate that tomography (planigraphy) is superior to all other methods for the roentgenologic demonstration of valvular and other cardiac calcification [15, 44]

Fluoroscopically, the calcified valves appear as dense nodular pulsating shadows which are described as dancing in a jerky fashion Their excursion is greater than that of the cardiac borders (1 to 2 cm) and is best observed in the oblique views and by roentgenkymography They are not apparently affected by deep respiration The calcified valves are seen slightly to the left of the midline (in a slight right oblique position which removes them from the dense spine shadow) and in the lowest

third of the cardiac shadow near the junction with the middle third. The mitral valve is in the posterior third of the cardiac shadow and the aortic valve slightly anterior and caudad to it. The motion of these shadows is rotatory or elliptical, their direction being downward and toward the apex in systole and upward and toward the midline in diastole. Both valves may be calcified. Calcification of the annulus fibrosus[24] may be distinguished from calcification of the cusps by a tendency to ring-like forms and less pulsation (Fig. 118). The discovery of calcification of the aortic valve on roentgenologic examination does not necessarily indicate aortic stenosis. But such discovery is a strong diagnostic confirmation when aortic stenosis is suspected clinically. Calcification of the valves may be distinguished from calcified pericardium, calcified tumors, thrombi or aneurysms of the heart by the characteristic shape, position and pulsation of the calcified valves. They can be distinguished from calcified lymph nodes and other extracardiac calcifications by the fact that calcified valvular shadows cannot be projected outside the cardiac outlines on rotating the patient.

The Electrocardiogram in Aortic Stenosis

The electrocardiogram may be normal or show only a left axis deviation if there is no associated mitral stenosis. In severe cases there is evidence of left ventricular hypertrophy. Not infrequently there are (1) permanent or transient severe conduction disturbances and (2) abnormalities of the T waves and RS-T transitions similar to those seen in coronary artery disease.

The conduction disturbances in order of frequency appear to be left bundle branch block, intraventricular conduction defects, partial and complete heart block.[■] I have seen cases in which the electrocardiograms showed first one, then another and even a third of these disturbances at different times.

Atrial fibrillation is uncommon in well compensated pure monovalvular aortic stenosis except when it is due to associated mitral stenosis.[■] However, it has been noted in as many as 30 per cent of one series of cases,[8] probably due to associated lesions.

The Ballistocardiogram

Distinctive angulation or bowing of the J-K segment of the low frequency ballistocardiogram has been described in cases of aortic stenosis with or without insufficiency.[■] The K wave may be small and M prominent. Likoff et al[■] stressed a shallow K wave as the most constant finding.

COMPLICATIONS OF AORTIC STENOSIS

Heart failure occurs most often and is the commonest cause of death. Sudden death is not infrequent. Bacterial endocarditis is uncommon except in cases with predominant aortic insufficiency. Myocardial infarction with or without coronary thrombosis is occasionally observed. The Adams-Stokes syndrome may be a fatal complication. Bronchopneumonia, pulmonary infarction and acute pulmonary edema are occasional complications which may result fatally.

DIAGNOSIS

The diagnosis is simple if the classic cardinal criteria are satisfied, namely: (1) a loud, rough aortic systolic murmur, (2) an aortic systolic thrill, (3) absent or faint second aortic sound and (4) a characteristic small delayed pulse. The most common oversight is failure to palpate the chest wall for a thrill. The importance of a high-pitched squeaking systolic murmur in the diagnosis of aortic stenosis and calcification of the aortic valve has been stressed by Braun and Comeau.[19] When an associated mitral stenosis dominates the clinical features, an aortic stenosis may be easily overlooked unless two or more of these signs are present. Usually the murmur and thrill suffice to justify the diagnosis. The finding of calcification of the aortic valves on roentgenologic examination and the characteristic pulse tracings are confirmatory. The presence of an aortic murmur for many years in a middle-aged or elderly male should suggest the possibility of calcific aortic stenosis, especially if such a murmur is associated with a history of angina pectoris, dizziness or syncope. In the absence of syphilis or a positive Wassermann reaction and in the absence of the peripheral signs of aortic insufficiency, a combined systolic and diastolic murmur over the aortic area should suggest calcific aortic stenosis. In cases of mild aortic stenosis a diagnosis of calcific aortic stenosis may have to be ventured merely on the basis of a rough aortic systolic murmur and the fluoroscopic demonstration of a calcified aortic valve. To confirm the diagnosis of aortic stenosis and to determine its severity in patients in whom an aortic commissurotomy is being considered

left and right heart catheterization and measurement of the left ventricular aortic gradient may be undertaken (pp 77 and 699)

PROGNOSIS

Individuals with pure aortic stenosis, especially the calcific form of the disease have a good prognosis and are usually long lived The outlook remains favorable only so long as compensation is maintained and there are no symptoms Clawson Bell and Hartzell[15] found the average age at death of 29 cases with predominant aortic stenosis to be 55 8 years as compared with an average age of 41 7 years for mitral stenosis Clawson Noble and Lufkin[16] found that the majority of their 200 cases survived until the seventh decade or later

The occurrence of angina pectoris or syncopal attacks is unfavorable Once heart failure develops the prognosis is extremely poor and the course of the disease is rapidly progressive Contratto and Levine[17] noted the occurrence of death in aortic stenosis on an average of 23 months after the onset of dyspnea, 9 3 months after the onset of peripheral edema 9 months after the onset of syncope 6 months after the appearance of râles in the lungs and 4 months after the development of the first attack of pulmonary edema

TREATMENT

MEDICAL MANAGEMENT

The medical treatment of aortic stenosis is essentially symptomatic Restriction of physical activities may be necessary when there are attacks of angina pectoris or syncope or when congestive heart failure develops The treatment of these complications has been considered in previous chapters

SURGICAL TREATMENT

Following experimental studies various procedures have been devised to correct the aortic stenosis by surgical means [41 43 45 4 52 44] As with mitral stenosis it would appear that the strain imposed on the heart could be alleviated by enlarging the stenotic opening in the aortic valve

Indications and Choice of Patient for Aortic Valvulotomy

In general aortic valvulotomy (commissurotomy) appears indicated when aortic stenosis is very severe when there is a high gradient between the left ventricle and aorta (over 50 mm Hg), and there are clinical manifestations which are due directly or indirectly to the stenosis Actually it is difficult to determine accurately the severity of the stenosis before operation Attempts are being made to determine the pressures within the left ventricle and the aorta by means of catheters passed through a needle inserted into the left atrium by way of the bronchus or thoracic wall, and thereby measuring the pressures in the left ventricle and aorta thus calculating the gradient The gradient between the left ventricle and aorta can be determined at the time of operation for a concomitant mitral stenosis

In practice the selection of patients for aortic valvulotomy is determined by a consideration of the symptoms and the clinical stage of the disease Patients who are well compensated and are asymptomatic are not regarded as candidates for the operation A second group of patients with well defined manifestations of aortic stenosis complain only of general heart consciousness or vague precordial distress palpitation fatigability or mild dyspnea on more than ordinary exertion This is a very favorable group for aortic valvulotomy if one can carefully exclude other causes for these symptoms and if one is reasonably certain that they are due to the aortic stenosis Similarly aortic valvulotomy is regarded as indicated in patients with angina pectoris or syncope when these manifestations are due to the stenosis But it should be reemphasized that coronary atherosclerosis with narrowing or occlusion is not uncommon in patients with aortic stenosis, particularly in those patients past middle age who have the calcific aortic stenosis Similarly other causes for syncope should be excluded before attributing this symptom to the stenosis and before regarding it as a clear indication for surgical therapy

The outlook is so poor after patients with aortic stenosis have developed definite left sided heart failure, and especially after right sided heart failure has appeared that aortic valvulotomy may appear to offer the only hope for improvement Harken[38] found that of 34 patients with aortic stenosis to whom aortic surgery was recommended because they had developed left ventricular failure syncope or angina pectoris but who refused operation 30 were dead in less than six months

Therefore the indication for surgery in these groups of cases is partly a negative one in that there is very little to lose and perhaps much to gain Unfortunately the mortality rises progressively with left and right sided heart failure respectively and the results become proportionately less favorable since myocardial damage as well as the mechanical effect of the stenosis accounts for the patient s symptoms Furthermore in about 20 per cent of patients with severe clinical manifestations of aortic stenosis the aortic valve is so calcified and fixed that the aortic orifice cannot be materially dilated[44]

Aortic valvulotomy for aortic stenosis offers less of a problem when the aortic stenosis is combined with mitral stenosis and a mitral commissurotomy appears indicated The aortic valvulotomy may be performed even when there is some degree of mitral insufficiency provided that the mitral stenosis is the dominant lesion Relief of the aortic stenosis may actually diminish the degree of mitral regurgitation since the left ventricular pressure is diminished

Aortic valvulotomy may be performed for an aortic stenosis even when there is a diastolic murmur denoting concomitant aortic insufficiency provided that the aortic stenosis is definitely the predominant lesion and there are no hemodynamic evidences of a free aortic regurgitation Aortic valvulotomy is indicated whether the stenosis is rheumatic or congenital and the association of a coarctation of the aorta is not a contraindication

Contraindications

At the present time aortic valvulotomy should not be performed if there is a marked aortic insufficiency associated with the stenosis if there is complete heart block if there is evidence of infection or intercurrent diseases which would make the patient a poor risk or if there is advanced right heart failure which does not respond to therapy Patients beyond the age of 50 are not regarded as desirable candidates for aortic valvulotomy

Technique of Operation

The patients with left or right sided heart failure should be treated by bed rest digitalis low sodium intake and diuretics until maximum benefit has been obtained but without undue delay of the operation Frequently heart failure in aortic stenosis is not readily responsive to medical treatment

The patient is maintained by endotracheal anesthesia with oxygen and ether after induction with Pentothal sodium or cyclopropane The chest may be entered through an anterolateral incision in the fifth intercostal space the incision extending from the left border of the sternum to the posterior axillary line Or the chest may be entered through a transverse sternal splitting incision which exposes the ascending aorta and heart anteriorly Bailey[3] employs a right thoracic approach in cases of combined mitral and aortic stenosis (p 674)

There is no universal agreement as to whether the valve should be dilated by an instrument inserted through the left ventricle or through the aorta just above the aortic valve Bailey and associates[4] have operated on 170 patients with aortic stenosis by the ventricular route using a dilator with parallel blades Muller[45] made a small stab wound in an avascular area of the left ventricle near the apex and inserted a special aortic valvulotome with dilating components When the surgeon believes that he has dilated the aortic valve satisfactorily the valvulotome is withdrawn the pressures in the aorta and left ventricle are measured and if the gradient has been sufficiently reduced the stab wound in the ventricle is closed with interrupted sutures The gradient should be reduced at least below 50 mm Hg but preferably as close to zero as possible If the gradient is still too high the valvulotome should be introduced again and further dilatation of the valve effected

Bailey[4, 5] now prefers a retrograde approach by the transaortic route and has operated on 47 patients with aortic stenosis by this technique The aortic wall is pinched off with the aid of a curved Potts toothed clamp or a special type of Satinsky clamp and a pouch of pericardium is sewed to an opening made in this excluded portion of the aortic wall A purse string suture is placed around the periphery of the opening to maintain homeostasis A finger is then inserted through the pouch and the aortic opening into the aorta and aortic valve As with mitral commissurotomy the finger fractures the commissures or separates the cusps in the majority of cases If necessary a mitral guillotine knife or similar knife carried along the finger may be used to separate unyielding commissures A somewhat similar transaortic technique has been employed by Fell[11] to

dilate stenotic aortic valves in 8 patients varying in age from three months to 50 years He utilized a dilator calibrated to 24 mm

In patients operated on for mitral stenosis, the coexistence of severe aortic stenosis may be determined or verified at operation by palpation of a systolic thrill near the stenotic valve and by measurement of pressures in the left ventricle and aorta Either the mitral or aortic stenosis may be corrected first On theoretical grounds it might appear that relief of the aortic stenosis may improve coronary artery perfusion, diminish any mitral regurgitation by diminishing left ventricular pressure and reduce the danger of overloading the left ventricle when the mitral valve is dilated However, Bailey usually dilates the mitral valve first, and Muller[52] recommends dilating first the valve which is most severely affected

Another method used to correct experimental aortic stenosis consists in a permanent by pass of the aortic valve A lucite tube, placed in the apex of the left ventricle conducts blood through a modified Hufnagel valve and into the thoracic aorta[54]

Surgical Mortality and Results

In the largest series, that of Bailey et al,[4] the operative mortality was 25 per cent (in 173 cases) by the ventricular route and 14 per cent (in 47 cases) by the transaortic route[3, 4a] However, the mortality was significantly lower in patients with combined aortic and mitral stenosis In such cases of combined valvular disease, the mortality was 18 4 per cent among 87 patients operated on by the transventricular route and only 1 death among 14 *patients operated on by the transaortic* route Muller[52] operated on 26 patients with pure aortic stenosis (with or without mild *aortic insufficiency), 10 patients with aortic* and mitral stenosis and 1 with aortic stenosis and coarctation of the aorta There were 7 operative deaths (27%) among those with aortic stenosis alone, and 3 deaths (30%) among those with aortic and mitral stenosis Glover[30] reported that the mortality was only 8 per cent in patients with early symptoms with a favorable result in about 75 per cent The mortality rose to 44 per cent when there was a history of episodes of pulmonary congestion and to 85 per cent in the presence of frank congestive heart failure

The surgical complications and causes of mortality are chiefly ventricular fibrillation, cardiac arrest, hemorrhage from the incised ventricle and the production of frank aortic insufficiency Cerebral and pulmonary embolism and temporary or persistent complete heart block or bundle branch block have also occurred In a number of cases bacterial endocarditis has developed within a few months after aortic commissurotomy[4a]

It is still too early to evaluate the clinical results of aortic valvulotomy Excellent results have been claimed in about 75 per cent of cases Evaluation depends chiefly on reports of subjective alleviation of symptoms such as palpitation, dyspnea, orthopnea, fatigability, poor exercise tolerance, syncope and angina pectoris[4a] Objective improvement was denoted by pressure changes and reduction in left ventricular aortic gradient at operation and by reduction in cardiac size postoperatively The aortic systolic murmur does not disappear but a diastolic murmur may appear or become louder

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Chapter 29

TRICUSPID AND PULMONIC VALVULAR DISEASE

TRICUSPID VALVULAR DISEASE

ETIOLOGY

Tricuspid insufficiency is usually a functional disturbance but may be due to organic disease of the valve[11]

Organic tricuspid insufficiency is almost always caused by rheumatic fever, but it may occasionally result from trauma which tears a cusp or ruptures its chordae or papillary muscle Rarely bacterial endocarditis causes or increases a tricuspid insufficiency Malignant carcinoid of the small intestine may be associated with scarring of the tricuspid valve and tricuspid insufficiency (p 1042) Congenital tricuspid insufficiency is rare, and may be due to incomplete differentiation of the cusps or to a downward displacement of the right ventricle (Ebstein type) (p 788)

Frequent involvement of the tricuspid valve in rheumatic heart disease was noted by Sansom[31] There is almost always concomitant rheumatic mitral disease and often also aortic valvular involvement Gross and Friedberg[16] found microscopic evidence of rheumatic inflammation in the tricuspid valve almost as often as in the mitral but significant insufficiency or stenosis is uncommon

Functional tricuspid insufficiency occurs in a great variety of conditions associated with failure and dilatation of the right ventricle When the right ventricle fails the tricuspid valve becomes insufficient for two reasons (1) Weakness of the right ventricular contraction removes the important muscular factor normally necessary to close the tricuspid orifice completely[20] For even normally there is a slight physiologic tricuspid insufficiency because the tricuspid leaflets are not quite large enough to close the tricuspid orifice Effective muscular contraction which narrows the tricuspid ring is important for complete closure of the tricuspid valve Atrial fibrillation usually present in functional tricuspid insufficiency, may intensify the insufficiency, since atrial contraction is required for normal closure of the atrioventricular valves[26] (2) Failure of the right ventricle is associated with enlargement of its chamber and consequent retraction of the papillary muscles and their attached chordae tendineae from the tricuspid valve Thus the tricuspid leaflets are held taut within the ventricular chamber and are unable to move sufficiently to close the orifice At the same time dilatation of the right ventricle stretches the tricuspid ring and enlarges the orifice

Tricuspid stenosis is less common than tricuspid insufficiency but not so rare as was formerly believed[9, 2, 28, 14, 5] As a rule insufficiency is associated with tricuspid stenosis Tricuspid stenosis is almost always associated with a more severe mitral stenosis the latter being present in all 30 cases of tricuspid stenosis reported by Dressler and Fischer,[9] and in 181 of the 195 cases reported by Futcher[18] Aortic insufficiency or stenosis is also associated in one half to two thirds of the cases Occasionally tricuspid stenosis may occur as an isolated lesion[14, 11, 19] g, in 14 of the 187 cases collected by Herrick[18] Tricuspid stenosis may be associated with disease of the other three valves[17]

Tricuspid stenosis may be congenital or acquired The congenital lesion is very rare and is due to adhesion of the free borders of the valve More often there is an atresia of the tricuspid valve with ventricular malformation

Acquired tricuspid stenosis is almost invariably due to rheumatic fever but occasionally a functional tricuspid stenosis results from bacterial vegetations thrombi

or tumors projecting into the tricuspid orifice The obstructing vegetations which are polypoid and massive occur in bacterial endocarditis Obstructing atrial thrombi occur rarely in cases of heart failure with atrial fibrillation[47] or in cases of myocardial infarction with a mural thrombus occluding the tricuspid valve from below The tumors are usually primary myxoma or sarcoma or secondary metastases of hypernephroma sarcoma of the testis carcinoma of the thyroid or other neoplasms

Tricuspid stenosis has been found by Smith and Levine[42] in 10 per cent of 340 and by Cooke and White[8] in 15 per cent of 217 autopsied cases of rheumatic heart disease These and other observers have noted additional cases of rheumatic involvement of the tricuspid valve without significant deformity In still other cases of rheumatic tricuspid valvular disease no differentiation is made between stenosis and insufficiency Among 147 autopsied cases of rheumatic heart disease reported by Aceves and Carral[2] 50 per cent had some tricuspid involvement and 33 per cent (49 cases) had a valvular deformity classified as tricuspid insufficiency Of the latter 49 cases 11 disclosed predominant stenosis and another 11 equally marked stenosis and insufficiency Tricuspid valvular disease was found in 17 per cent of a large series of patients operated on for mitral and aortic valvular disease In 11 per cent predominant tricuspid stenosis was recognized by direct digital examination[2] Several cases of isolated tricuspid stenosis have been reported[19, 14]

Age and Sex

These are the same as in patients with other rheumatic valvular lesions The usual age is between 25 and 40 for the organic rheumatic cases of tricuspid valvular disease but occasional cases are encountered in persons beyond the age of 50 There is a distinct predominance of females especially among those with pronounced tricuspid stenosis

PATHOLOGY

The pathologic findings in the valves are described in the chapters on the causative disease (i e rheumatic fever congenital heart disease etc) In the rheumatic cases the cusps undergo inflammatory swelling and thickening which interfere with their proper coaptation Closure of the tricuspid orifice is further impaired by shortening and retraction of the cusps and their chordae Tricuspid insufficiency is enhanced when dilatation of the right ventricle is associated with concomitant dilatation of the tricuspid ring Tricuspid stenosis is the predominating disturbance when rheumatic inflammation and scarring causes adhesion of the cusps to each other This leads to a single fused cylindrical or conical curtain or to a buttonhole type of stenosis with a rigid slot like aperture Some degree of tricuspid insufficiency is associated The associated mitral stenosis is almost always more pronounced than the tricuspid stenosis Instead of the normal circumference of 11 to 13 cm the tricuspid ostium measures usually 15 to 17 cm or more in tricuspid insufficiency or 8 cm or less in tricuspid stenosis With severe stenosis the tricuspid valve area may be less than 1 sq cm

Bacterial endocarditis may enhance a rheumatic tricuspid stenosis by forming a large obstructing vegetation or increase an insufficiency by destruction of a cusp or chordae However the tricuspid valve is uncommonly involved in bacterial endocarditis Following intravenous injection of heroin in addicts there may occur an isolated staphylococcus or other bacterial or yeast endocarditis of the tricuspid valve

The Heart

The size of the heart and of the individual chambers is determined in part by associated lesions The right atrium is dilated and hypertrophied with both tricuspid insufficiency and stenosis In tricuspid stenosis the right atrium may be so enormous that it appears as a supplemental heart and in Taussig's[44] case it was the only hypertrophied chamber Sometimes the dilated right atrium appears as a huge fibrous sac in which the muscle has undergone atrophy

The right ventricle is dilated and hypertrophied both in organic and functional tricuspid insufficiency In the presence of pronounced tricuspid stenosis the right ventricle may be normal in size or only slightly hypertrophied The associated mitral stenosis often causes right ventricular hypertrophy of some degree but this is less pronounced when the tricuspid stenosis is marked than when it is slight In a recent observed case of pure tricuspid stenosis the right atrium was the predominant cardiac chamber whereas the right ventricle appeared atrophic

The left atrium is usually dilated and hypertrophied in organic tricuspid stenosis or insufficiency because of the concomitant mitral stenosis. In cases of functional tricuspid insufficiency the left atrium may be dilated and hypertrophied if left-sided heart failure preceded failure of the right heart, but not if the latter is due to cor pulmonale.

The size of the left ventricle is determined by the presence, order of development and predominance of mitral stenosis or of an aortic valvular lesion.

The *venae cavae* are prominently dilated and may form a continuous sac with the dilated right atrium. As a result of venous stasis, the internal viscera, particularly the liver, spleen and kidneys, show severe chronic passive congestion. Cardiac cirrhosis of the liver is more frequent than in other forms of valvular disease and heart failure.

PATHOLOGIC PHYSIOLOGY

Both with tricuspid stenosis and insufficiency there is an increased diastolic volume of blood in the right atrium. In the former it is due to incomplete emptying through the narrowed valvular orifice, in the latter to regurgitation of blood into the atrium during right ventricular contraction. The increased stretch results in a more forceful atrial contraction with at least a temporary restoration of normal output. During this process of compensation the right atrium becomes dilated and eventually hypertrophied.

Because of the limited compensatory capacity of the thin right atrial wall, systemic venous distention occurs early. This serves to diminish the outflow from the right side of the heart and reduces or prevents pulmonary engorgement. When tricuspid stenosis is the predominant lesion, its effect is somewhat similar to that of constrictive pericarditis in that it obstructs the inflow of blood into the right ventricle.

The dynamics of tricuspid lesions may be modified and are often overshadowed by those of associated mitral or aortic valvular disease. In the instances of functional tricuspid insufficiency the prevailing circulatory dynamics are determined by the conditions which produce ventricular dilatation and failure.

Intracardiac catheterization has disclosed characteristic pressure tracings in cases of tricuspid insufficiency.[3, 11, 21] In cases of right-sided heart failure with competent tricuspid valve there is a pronounced fall in atrial pressure early in ventricular systole due to descent of the tricuspid valve. But when the tricuspid valve is insufficient, blood spurts back into the atrium during systole and the atrial pressure is unchanged or rises instead of falling. This positive pressure wave, persisting throughout systole, produces a peak-dome or peak-plateau contour. The mean atrial pressure is markedly elevated and increases further with exercise. The calculated pulmonary resistance was much higher in a group of patients with mitral disease and tricuspid insufficiency than in those without tricuspid insufficiency.[48] In pure tricuspid stenosis the striking feature of the atrial pressure tracing is the presence of giant "a" waves.

The right atrial pressure is elevated, often to a mean pressure between 10 and 25 mm Hg instead of the normal of 3 mm Hg.[21] The atrial pressure rises further with the onset of ventricular contraction in tricuspid insufficiency but not in pure tricuspid stenosis.[11] Not only the right ventricular systolic but also the right ventricular diastolic pressure is elevated, denoting right ventricular failure.

Normally, with opening of the tricuspid valve, right atrial and ventricular pressures are essentially equal in diastole, i.e., there is virtually no gradient. In tricuspid stenosis there is an abnormal pressure gradient between right atrial mean pressure (or Z-point pressure) and the diastolic pressure in the right ventricle.[11, 6, 34] The gradient is increased by exercise. Such a diastolic gradient is not present in tricuspid insufficiency and distinguishes "pure" stenosis from "pure" insufficiency of the tricuspid valve.

CLINICAL FEATURES

The clinical picture of tricuspid valvular disease resembles that of advanced right-sided heart failure with systemic venous engorgement. In cases of organic tricuspid disease there is usually a preceding period of known mitral stenosis or of mitral and aortic valvular disease, with or without left-sided heart failure. When organic tricuspid disease is added, the clinical picture may be indistinguishable from that of mitral and aortic valvular disease

with heart failure or it may be dominated by the effects of the tricuspid lesion

The clinical features of pure tricuspid insufficiency may be gleaned from rare cases of traumatic origin Todd[15] reported the case of a man of 21 who following a stab wound in the right chest suffered a rupture of the chordae tendineae of the anterior cusp of the tricuspid valve Two and a half years later he was in advanced right heart failure with hepatic enlargement widespread anasarca and ascites

In cases of functional tricuspid insufficiency the clinical picture is characterized by the combination of left and right-sided heart failure or of primary pulmonary disease with secondary right heart failure

In cases of *pure or predominant tricuspid stenosis* there may be virtually no subjective symptoms except pain in the right upper quadrant of the abdomen due to an enlarged tender liver Physical signs include pulsating cervical veins with prominent giant a waves a pulsating liver a rumbling diastolic murmur at the left border of the sternum and apex sometimes with an opening snap P_2 is not accentuated Roentgenologic examination shows a greatly enlarged right atrium producing a horizontal shelf in the left anterior oblique view Atrial fibrillation edema and ascites are late developments

Symptoms of Tricuspid Valvular Disease

Dyspnea on exertion is the commonest subjective symptom probably due to pulmonary congestion caused by a concomitant mitral stenosis or other lesion producing left sided failure However the remarkable feature of tricuspid disease is the relative freedom from orthopnea and paroxysmal dyspnea Careful questioning and observation does disclose orthopnea in most patients but the degree is surprisingly mild for many of these patients with edema and ascites are seen to be lying flat in bed without apparent discomfort Sometimes the development of tricuspid stenosis or insufficiency is documented by partial or complete relief of preceding dyspnea and orthopnea due to left sided heart failure This relief in pulmonary congestion is regarded as the consequence of diminished right ventricular output into the lungs because of the tricuspid lesion

Persistence of dyspnea in the presence of tricuspid valvular disease may be due to hydrothorax or the pressure of abdominal ascites as well as to pulmonary congestion secondary to mitral valvular disease When functional tricuspid insufficiency follows cor pulmonale and right heart failure dyspnea persists because of the primary pulmonary disease

Other subjective symptoms include anorexia nausea eructations vomiting and abdominal pain due to chronic passive congestion of the gastrointestinal tract to enlargement of the liver or to ascites Rarely hematemesis or melena occurs from secondary ulceration of the congested inflamed mucosa of the gastrointestinal tract

In cases of isolated pure tricuspid stenosis there may be no subjective symptoms or only fatigability without dyspnea cyanosis edema or ascites

Objective Signs

Hepatic enlargement is a constant finding The liver may be huge There is usually a systolic liver pulsation in cases of tricuspid insufficiency or a presystolic pulsation in cases of tricuspid stenosis (infra) In my experience most physicians overlook hepatic pulsation even when it is readily ascertainable Pulsating liver can be distinguished from a transmitted pulsation by simultaneous palpation of the liver and carotid artery[37] In tricuspid insufficiency hepatic pulsation is felt late in systole after the carotid pulsation

Venous engorgement especially of the cervical veins is a striking feature of tricuspid disease There is a pronounced systolic pulsation with tricuspid insufficiency and a characteristic double pulsation with giant a waves in tricuspid stenosis provided the rhythm is regular Similar venous distention and pulsation may be visible in the more peripheral veins such as the basilic veins and those in the dorsum of the hands[16] The *venous pressure* is greatly elevated and increases with pressure over the right upper quadrant of the abdomen (hepatojugular reflux) The *circulation time* is increased

Ascites is a predominant manifestation Its relatively long duration and its recurrence despite repeated abdominal tappings are characteristic features However ascites has been absent in the cases of isolated tricuspid stenosis without associated valvular lesions

Edema is present in most cases of severe tricuspid stenosis or insufficiency In cases of tricuspid stenosis and often in cases of tricuspid insufficiency peripheral edema may be absent

or relatively slight in contrast with the usual findings in right-sided heart failure In the series of 21 cases studied by Muller and Shillingford [31] peripheral edema was severe in 6, moderate in 8, slight in 3 and absent in 4 of the patients

Effusions in the pleural cavities are common in all types of tricuspid valvular disease

The explanation for the relatively early and disproportionate ascites in tricuspid stenosis is unknown Extreme rapid and prolonged congestion of the liver may account for the predominant ascites reminiscent of hepatic cirrhosis Eventually edema of variable degree develops in most cases of tricuspid disease *Hypoproteinemia* due to hepatic dysfunction is an important contributory factor The edema may also involve the face, since patients with tricuspid stenosis do not usually suffer from orthopnea and lie flat in bed

Cyanosis is a frequent finding in advanced cases but Sepulveda and Lukas[41] noted it in only 15 per cent of their patients with tricuspid insufficiency Cyanosis is due essentially to longstanding pulmonary congestion secondary to mitral stenosis or to preceding pulmonary disease Pulmonary infarction may be a contributing or primary causative factor Pronounced slowing of the blood stream with peripheral stasis may also contribute to cyanosis by increasing the tissue extraction of oxygen from the capillaries

Cyanosis is usually more pronounced and dyspnea less pronounced in cases of tricuspid and mitral stenosis than in mitral stenosis alone This may denote that the relief of pulmonary engorgement afforded by the tricuspid lesion diminishes the rigidity of the lung and thereby alleviates dyspnea On the other hand in the presence of tricuspid disease, the associated mitral stenosis is almost always very severe and the fibrosis and thickening of the pulmonary alveolar septa are pronounced The latter changes impair aeration of the blood Thus arterial anoxemia and cyanosis result from poor aeration of the pulmonary capillary blood, even though pulmonary compliance improves as the vascular congestion diminishes Secondary *polycythemia* may develop as a compensation to the anoxemia

Icterus or a subicteric tint is often combined with the cyanosis in the cases of organic tricuspid disease The resulting yellowish blue or olive coloration often suggests the diagnosis [9, 51] The jaundice is probably due to hepatic dysfunction caused by longstanding congestion and fibrosis of the liver Frequent *pulmonary infarcts* seen in organic tricuspid disease have also been held responsible as a contributing causative factor (p 206)

Systolic or Positive Venous Pulse in Tricuspid Insufficiency The right atrium is never completely emptied and there is an elevated pressure In addition blood is regurgitated into this chamber during ventricular systole As a result of the persistent atrial stasis and the impulse of the regurgitant stream the cervical veins remain filled and expand during systole The negative wave or depression "x" which is present in the normal jugular venous pulse (p 72) disappears This results in the so-called *positive venous pulse* or *ventricular venous pulse* of tricuspid insufficiency The absence of the x depression produces a characteristic plateau in systole [9] The pulse is often visible, without the aid of tracings, as a broad systolic wave ascending the neck along the course of the internal jugular vein up to the very ear lobe The external jugular vein may be too distended to disclose pulsation In less severe cases of tricuspid insufficiency the jugular phlebogram may show a positive systolic wave after an abbreviated x depression and before the v wave [27, 31]

The right atrial pulse similarly shows a diminution in the x depression or replacement by a plateau or positive wave [9, 11, 23] Moderate rises of venous pressure are associated with an impairment of systolic (x) depression whereas with greater increases in venous pressure a positive systolic wave replaces the x descent

When tricuspid regurgitation is associated with tricuspid stenosis the appearance of the positive wave after the "c" wave is delayed the rise of the wave is slower the peak occurs later and the diastolic collapse is slower [10]

A positive venous pulse may be insignificant in tricuspid insufficiency if the right atrium is greatly dilated and the regurgitant stream has little effect on its large content On the other hand a positive venous pulse may be observed in the absence of tricuspid insufficiency when there is atrial fibrillation with right sided heart failure and advanced venous stasis [22] But the systolic pulsation is rarely as well defined as in tricuspid insufficiency

Atrial Venous Pulsation in Tricuspid Stenosis In tricuspid stenosis the cervical venous pulse

often shows an accentuated 'a' wave due to the increased force of contraction of the hypertrophied right atrium. In addition the obstruction at the tricuspid orifice may cause a regurgitation of blood from the right atrium into the cervical veins. These factors cause a rise in venous pressure and a consequent venous pulsation during atrial systole. This is known as the *atrial venous pulse* and is a characteristic feature of tricuspid stenosis. But it may occur if there is pronounced left atrial hypertrophy with a large interatrial septal defect. It may be absent if the atria are fibrillating.

Sometimes there is a distinctly visible *double* pulsation of the cervical veins, one synchronous with ventricular systole and one presystolic in time. The latter denotes tricuspid stenosis and the former concomitant insufficiency or pronounced right atrial stasis behind the tricuspid obstruction. I have also observed distinct double jugular venous pulsations in a case of rupture of a congenital aneurysm of the sinus of Valsalva into the right atrium and in two cases of coronary heart disease with left- and right-sided heart failure and tricuspid insufficiency, with regular sinus rhythm.

Systolic (Ventricular) and Atrial Liver Pulse. In cases of tricuspid insufficiency there is usually a palpable pulsation of the liver during ventricular systole. It is explained by regurgitation of blood from the right ventricle into the atrium. This leads to a transmitted pulse into the inferior vena cava, hepatic veins and their tributaries, corresponding to the systolic jugular pulse.

Clinically the systolic liver pulse is best noted as an expansile sensation when the liver is examined bimanually, one palm being held over the posterolateral surface of the lower right axilla and the other anteriorly over the right upper quadrant of the abdomen, i.e., over the liver. The patient should hold his breath. This pulsation must be differentiated from the pulsations of a large right ventricle transmitted through the diaphragm or from similar transmitted pulsations from a dynamic or aneurysmal abdominal aorta. But these pulsations are rarely expansile and strike only one of the two examining hands. A systolic liver pulse may be absent in tricuspid insufficiency if the regurgitant flow is too slight, if there is a hugely dilated right atrium or if longstanding passive congestion has produced a pseudocirrhotic liver which cannot pulsate.

A systolic pulsation of the spleen has been described in tricuspid insufficiency.[43]

In *tricuspid stenosis* there may be a *presystolic or atrial liver pulse* corresponding to the *atrial venous pulse* and due to a similar mechanism.[15, 34] This is best demonstrated by graphic registration but may be recognized by bimanual palpation. A double liver pulse may be encountered when there is a combination of tricuspid stenosis and insufficiency, one pulsation being due to atrial contraction and the other to ventricular systole, which causes a regurgitant impulse in the right atrium and inferior vena caval tributaries. Grishman and associates[15] have recently emphasized that the presystolic liver pulse is not specific for tricuspid stenosis but occurs also in a variety of other conditions. They described its occurrence in congenital heart disease, especially interatrial septal defect, in certain cases of myocarditis with congestive heart failure, in cor pulmonale and in chronic atrial flutter without organic heart disease. I have observed it in a case of rupture of a congenital aneurysm of the sinus of Valsalva into the right atrium, which was included in the series of Grishman et al. As in tricuspid stenosis, the presystolic liver pulse in these conditions is due to a pulse transmitted to the vena cava and liver by a rapid rise in pressure in the right atrium as a result of valvular obstruction or high resistance (pressure) in the right ventricle. Presystolic venous pulse is often but not invariably associated with presystolic liver pulse. Right ventricular enlargement and right ventricular failure are often but not always present in cases of pure tricuspid stenosis. Although the early diastolic 'v' wave is also exaggerated, it is not as prominent as the 'a' wave. Occasionally double pulsations corresponding to the 'a' and 'v' waves are palpable. But the late systolic pulsation of tricuspid insufficiency is not observed except when the presystolic liver pulse is due to tricuspid stenosis and insufficiency.

The Heart in Tricuspid Valvular Disease

The physical signs over the heart are often determined by the associated mitral stenosis or other valvular disease.

In cases of *tricuspid insufficiency* there may be a characteristic see-saw movement of the

chest wall [8] This is due to a propulsion of the lower right side of the sternal region by the pulsating liver while simultaneously ventricular systole causes a pronounced depression of the precordium The latter is due to the aspiratory effect on the chest wall of ventricular ejection of blood out of the thorax while the influx of blood into the heart is prevented by the regurgitant stream

Percussion reveals enlargement of the heart, especially to the right In cases of pronounced *tricuspid stenosis* the dilated and hypertrophied right atrium may occasionally cause the right border to reach the right midclavicular line

Auscultatory Findings These are determined by the tricuspid valvular disturbance and the usually associated valvular lesions *Tricuspid insufficiency* is accompanied by a systolic murmur which is best heard at the lower end of the sternum or left fourth interspace When there is marked right ventricular hypertrophy with clockwise rotation of the heart in tricuspid insufficiency and mitral stenosis the tricuspid murmur may extend toward the apex and be mistaken for the systolic murmur of mitral insufficiency This distinction is important when mitral stenosis must be differentiated from mitral insufficiency in patients being considered for mitral commissurotomy The systolic murmur of tricuspid insufficiency is often increased in intensity with deep inspiration whereas most systolic murmurs are diminished with deep inspiration [11, 31] The murmur may vary in intensity and often disappears with clinical improvement

A short, low pitched diastolic murmur immediately after the second sound, may be present in some instances of tricuspid insufficiency [30, 31] presumably due to associated tricuspid stenosis Rarely, if the murmur is loud it may be accompanied by a thrill In two patients with clinical evidence of tricuspid as well as rheumatic and aortic valvular disease a short loud high pitched, early diastolic snapping sound was heard at or below and to the right of the xiphoid process This abnormal sound was interpreted as the opening snap of the stenotic tricuspid valve [23, 33]

In the rare cases of *pure tricuspid stenosis* there is a low pitched rumbling diastolic murmur at the left border of the sternum It may also be audible at the apex and be mistaken for the murmur of mitral stenosis But unlike the loud second pulmonic sound in mitral stenosis, the second pulmonic sound is not accentuated in isolated tricuspid stenosis A rumbling diastolic murmur, loudest parasternally in the fourth and fifth left intercostal spaces and increased in intensity by inspiration, is usually heard also in the cases of tricuspid stenosis associated with mitral stenosis

Occasionally an accentuated second pulmonic sound present in cases of mitral stenosis or pulmonary hypertension due to pulmonary disease, becomes soft with the development of tricuspid insufficiency

Chronic atrial fibrillation of long standing is the rule in patients with advanced tricuspid valvular stenosis or insufficiency

A *reversal of the paradoxical pulse* may be observed in cases of tricuspid insufficiency Instead of the slight reduction in pulse volume with deep inspiration felt normally or the pronounced reduction associated with constrictive pericarditis (pulsus paradoxus), there is an increased pulse amplitude with deep inspiration and a diminution with expiration For the pulmonary vascular capacity increases little during inspiration, while the venous return and therefore the cardiac output are significantly augmented

Roentgen Ray Examination of the Heart

Right atrial enlargement is the most consistent distinctive finding [41] The enlarged right atrium produces a widening of the transverse diameter of the heart The right lower cardiac contour is displaced to the right In the right oblique position the enlarged right atrium encroaches on the most caudad portion of the right retrocardiac space Even though mitral stenosis is present, the enlarged right atrium may displace the barium-containing esophagus to the left The combination of left atrial enlargement due to mitral stenosis and of right atrial enlargement due to tricuspid stenosis may produce double atrial concentric contours on the right side of the cardiac silhouette In isolated tricuspid stenosis the huge right atrium forms a horizontal shelf like projection from the upper anterior cardiac contour in the left anterior oblique view There is no enlargement of the pulmonary artery or right ventricle and no pulmonary congestion

In cases of pronounced tricuspid insufficiency, with or without stenosis the right

ventricle as well as the right atrium is enlarged and the heart has a globular triangular or transverse configuration The size and shape of the left contours are determined by associated mitral and aortic disease

The vascular shadow of the superior vena cava is widened and pulsates in systole or presystole The right innominate vein may also appear prominent and may pulsate Occasionally also there is widening and pulsation of the left innominate vein below the medial end of the left clavicle The diaphragm may be elevated in systole by the pulsating liver when normally it is depressed

Angiocardiography

Angiocardiography may be helpful in demonstrating right atrial enlargement and in distinguishing it from enlargement of the left atrium A jet sign i e a filling defect in the opacified right atrium produced by the regurgitant stream has been noted in some cases[7] In tricuspid stenosis angiocardiography discloses a persistent sharp opacification of the right atrium in contrast with delayed and poor opacification of the right ventricle

The Electrocardiogram

The electrocardiogram is usually characterized by right axis deviation by inversion of the T_3 and often also of T_2 and frequently by the pattern of right ventricular hypertrophy in precordial leads (p 115) Particularly in tricuspid stenosis there may be wide notched and high voltage P waves when there is sinus rhythm A diphasic P wave in right precordial leads has been described by Ellis and Brown[10] as distinctive of tricuspid disease but it may occur with mitral stenosis alone (p 120) A delayed onset of the intrinsicoid deflection in V_1 and V_2 of more than 0 04 second has been observed in the majority of cases of tricuspid disease and frequently there is an rsR con figuration in V_1 denoting incomplete right bundle branch block A QRS complex in V_1 of small amplitude (less than 7 mm) with a delayed onset of the intrinsicoid deflection was the most consistent electrocardiographic feature distinguishing cases of mitral disease and tricuspid insufficiency from those without tricuspid insufficiency in the series of Sepulveda and Lukas[11] In cases of pure tricuspid stenosis without significant mitral stenosis a tall right atrial P wave is present without the above-mentioned changes of right ventricular hypertrophy[11] Atrial fibrillation occurs in most cases Tricuspid stenosis with nodal tachycardia and atrioventricular dissociation has been reported[3]

DIAGNOSIS

Tricuspid insufficiency should be suggested by the presence of a large pulsating liver and pulsating cervical veins The diagnosis is simpler if in addition atrial fibrillation edema ascites cyanosis and evidence of valvular heart disease or cor pulmonale are present A characteristic bluish yellow facies due to combined cyanosis and mild icterus in a patient with mitral stenosis should suggest the association of tricuspid disease Evidence of pronounced right heart failure with relatively little orthopnea should also suggest this diagnosis Prolonged venous congestion with hepatomegaly and recurrent ascites out of proportion to edema in a patient with mitral stenosis who has had seemingly adequate treatment usually denotes organic tricuspid disease

Confirmation of the diagnosis may be provided by the following (1) Right atrial pressure curves showing a sustained peak plateau or dome throughout systole in cases of tricuspid insufficiency (p 712) (2) graphic demonstration of a systolic liver pulse and a positive jugular venous pulse in cases of tricuspid insufficiency or of an atrial or double liver pulse and giant atrial jugular venous pulse in tricuspid stenosis (3) prominent enlargement of the right atrium in addition to changes due to associated cardiovalvular disease

Differentiation of organic from functional tricuspid insufficiency is difficult[8] but the latter may occasionally disappear with active treatment of the congestive heart failure

A definite diagnosis of tricuspid stenosis may assume practical importance because of the *possible need for its surgical correction* Tricuspid stenosis is indicated by pulsating cervical veins with giant a waves a large pulsating liver a low pitched rumbling diastolic murmur over the tricuspid and mitral regions a normal second pulmonic sound in cases of pure tricuspid stenosis without mitral stenosis and roentgenologic and electrocardiographic evidence of right atrial enlargement A definite diagnosis requires cardiac catheterization with recording of pressure curves from the right atria and ventricle The characteristic finding is a large gradient between the atrium and ventricle throughout ventricular diastole

COURSE AND PROGNOSIS

Patients with organic tricuspid valvular disease are often ambulant and experience relatively long periods of comfort even after venous engorgement hepatic enlargement and ascites appear

The comfort which is due to the absence of orthopnea and paroxysmal dyspnea, is only relative because activity is greatly limited and the patient must lead a life of semi invalidism or invalidism The manifestations of heart failure persist substantially longer in cases of tricuspid disease than in those of isolated mitral stenosis or of mitral and aortic disease On the other hand, the general outlook for organic tricuspid disease is less favorable than for other valvular disease in that heart failure and death occur at a much earlier age Organic tricuspid stenosis and insufficiency are almost always combined with mitral and aortic valvular disease and indicate as a rule, more severe and more extensive rheumatic inflammation than in cases of mitral and aortic disease alone This may account for the poorer prognosis in the former Death in tricuspid valvular disease eventually results from progressive right heart failure pulmonary embolism and infarction or bronchopulmonary infection

The outlook in cases of functional tricuspid insufficiency depends on the underlying disease responsible for the right heart failure Most often functional tricuspid insufficiency denotes the end stage of chronic valvular or pulmonary disease and is therefore of ominous significance But temporary improvement and disappearance of the valvular insufficiency occur frequently with adequate therapy

TREATMENT

The treatment is that of the underlying disease and of advanced right-sided heart failure (Chapter 11) Bed rest, extreme restriction of sodium intake digitalization and the administration of mercurial diuretics are the cardinal therapeutic measures With adequate diuresis, abdominal paracenteses to remove ascitic fluid may not be required Sometimes, however, this procedure must be repeated many times over a period of years in order to afford symptomatic relief Thoracentesis affords relief when a large hydrothorax is responsible for dyspnea

Surgical Treatment

Surgical treatment must be considered in cases of organic tricuspid stenosis[8, 19, 21] Since mitral stenosis is present in almost all cases, the problem of surgical correction arises in connection with the performance of a mitral commissurotomy, provided there is no

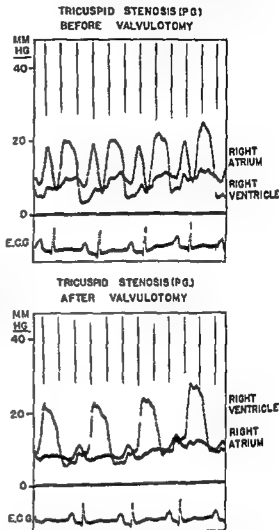


Fig 128 Simultaneous pressure pulses in right atrium and right ventricle obtained at operation in a case of isolated tricuspid stenosis before and after tricuspid valvulotomy Note tall atrial waves with pressure of 18 mm Hg during atrial systole After valvulotomy right atrial pressure markedly reduced and atrioventricular diastolic gradient almost eliminated (Private case operated on by Dr H A Nabatoff To be published by Gordon A J et al Am J Med)

other significant valvular deformity besides that of the mitral and tricuspid Tricuspid stenosis, without significant aortic or pulmonic valvular disease was found in 6 per cent of 66 cases of mitral stenosis[6] There is a possibility that an unsatisfactory result

from mitral commissurotomy may be due to failure to recognize and correct a concomitant tricuspid stenosis O Neill et al[5] performed a tricuspid commissurotomy four years after a mitral commissurotomy because of persistent signs of right sided heart failure and the clinical and hemodynamic features of pure tricuspid stenosis Following enlargement of the narrowed tricuspid valve edema and ascites disappeared As a rule correction of both the mitral and tricuspid stenosis is performed in a one-stage procedure both atria being exposed by an anterior thoracotomy and interatrial dissection Mitral commissurotomy is performed first to avoid excessive pulmonary congestion which might occur from increased right ventricular output if the tricuspid stenosis were relieved first In a recent case of isolated tricuspid stenosis operated on at Mount Sinai Hospital the right atrium appeared to form most of the cardiac mass Following tricuspid commissurotomy the right atrium promptly contracted in size the giant cervical venous pulsations disappeared and the right atrioventricular gradient was abolished (Fig 128) (See also p 674)

PULMONARY INSUFFICIENCY

ETIOLOGY AND PATHOLOGY

Organic insufficiency of the pulmonary valve is very rare[60] A relative or functional insufficiency is common but statistics as to its occurrence are extremely varied and unreliable[4] It is being observed with increasing frequency in patients with severe mitral stenosis and occasionally in cases of cor pulmonale Pulmonary insufficiency may be classified as *acquired* and *congenital* and the acquired lesions may be further subdivided into the *organic* and *functional* varieties The following causes of pulmonic insufficiency have been noted

I Acquired pulmonary insufficiency
- A Organic
  - 1 Bacterial endocarditis
  - 2 Rheumatic fever
  - 3 Pulmonary arteritis and valvulitis secondary to aortic aneurysm
  - 4 Syphilis of the pulmonary artery
- B Functional (pulmonary hypertension)
  - 1 Mitral stenosis
  - 2 Bronchopulmonary disease
  - 3 Primary pulmonary vascular occlusion (primary pulmonary hypertension)

II Congenital pulmonary insufficiency
- A Deficient or supernumerary pulmonic cusps
- B Congenital dilatation of the pulmonary artery

Acquired Organic Pulmonary Insufficiency

The commonest cause is a bacterial endocarditis involving the pulmonic valve Of 119 cases of pulmonic insufficiency taken from the literature and the autopsy records of Guy s Hospital Pitt[24] found that 60 were due to a bacterial endocarditis Insufficiency results from improper closure of the valves because of the attached vegetations or because of destruction or perforation of a cusp Multiple bacterial pulmonary emboli may arise from the vegetations Thayer[47] had noted the relative frequency with which the gonococcus attacks this valve and a similar tendency has been noted for the pneumococcus Bacterial endocarditis of the pulmonic valve is usually an isolated valvular lesion Of 26 cases Langeron and Gardère[4] found that the bacterial vegetations were confined to the pulmonic valve in 21 and associated with bacterial endocarditis of other valves in 5 I have not observed such localization in recent years

McGuire and McNamara[29] recently reported 3 cases of rheumatic pulmonary insufficiency one of them with slight pulmonic stenosis In all three cases the other valves were simultaneously affected I have occasionally seen gross rheumatic vegetations on the pulmonic cusps as well as mild microscopic inflammatory lesions of the valve and valve ring But except for slight thickening of these cusps I have never seen rheumatic valvular deformity of sufficient degree to interfere with their function

Occasionally a pulmonic insufficiency arises from pressure of an aortic aneurysm on the pulmonary artery at or just above the level of the pulmonary cusps especially the left cusp Inflammation of the pulmonary artery and cusp results from the pressure of contact or from perforation of the aneurysm The cusp subsequently becomes adherent to the arterial wall so that it can no longer aid in closing the pulmonic orifice

Syphilis of the pulmonary artery has been recorded in 66 cases, but according to Brenner[5] the diagnosis is established in only 15. This may produce pulmonic insufficiency by dilatation or aneurysm of the main vessel with concomitant dilatation of the pulmonic ring or by a widening of the commissure similar to that in luetic aortic insufficiency.

Many of the cases of pulmonic stenosis are accompanied by auscultatory or anatomic evidences of insufficiency.

Functional Pulmonic Insufficiency

The pulmonic valve becomes relatively insufficient when the pulmonic ring becomes dilated. Functional or relative pulmonic insufficiency has been known also as the insufficiency of high pressure in the pulmonary artery. The pulmonary hypertension is caused presumably by resistance to blood flow due to mitral valvular obstruction (p. 649), long standing disease of the lungs, or narrowing of the small pulmonary arteries and arterioles.

Congenital Pulmonary Insufficiency

Pulmonary insufficiency may be caused by two types of congenital defect, namely, *dilatation of the pulmonary artery* and *abnormality in the number of pulmonic cusps*. In 1000 cases of congenital heart disease studied by Abbott,[1] there were 8 primary cases of pulmonary insufficiency, 2 of which were due to valvular abnormalities and 6 to congenital dilatation of the pulmonary artery. There were 13 additional cases in which the pulmonic insufficiency was associated with other congenital defects of the heart. Kissin[1] noted that there were reports of 151 hearts with four pulmonic cusps but in only 3 of these cases was there sufficient functional disturbance to produce clinical signs. Insufficiency occurs despite the supernumerary cusp because the pulmonary artery and ring are greatly dilated.

Pulmonic insufficiency has been associated with isolated tricuspid pulmonary valve. Catheterization revealed a characteristic pulmonary artery pressure curve like the arterial curve in aortic insufficiency.[11] A decrescendo pulmonic diastolic murmur, prominent pulmonary arteries and hilar dance on fluoroscopy, and electrocardiographic evidence of right ventricular hypertrophy and prominent P waves were noted.

Dilatation of the pulmonary artery may occur as a primary solitary defect or in association with other major defects. Oppenheimer[33] reported 8 cases of idiopathic dilatation of the pulmonary artery and its branches, in 4 of which there was evidence of pulmonary insufficiency.

The Heart in Pulmonary Insufficiency

Two of the features common to all the varieties of pulmonic insufficiency are (1) hypertrophy of the right ventricle and (2) regurgitation of blood from the pulmonary artery into the right ventricle, with the consequent production of a diastolic murmur. In many cases there is also (3) a considerable dilatation of the pulmonary artery, the normal circumference of 6 to 8.5 cm. being exceeded in varying degree. Dilatation and hypertrophy of the right ventricle may develop as a consequence of the regurgitation of blood and may represent a compensatory phenomenon similar to that of the enlarged left ventricle in aortic insufficiency. Right ventricular hypertrophy with relatively little dilatation may, however, have preceded the onset of pulmonary insufficiency due to the increased resistance of pulmonary hypertension in chronic pulmonary disease.

CLINICAL FEATURES

Symptomatology

The symptomatology[4] is usually overshadowed by the primary disease of which the pulmonic insufficiency is a mere incident. Thus dyspnea on exertion, cough, mild or intense cyanosis, hemoptysis, somnolence, peripheral edema and ascites may also be attributed to the underlying pulmonary, valvular or congenital heart disease independent of the pulmonary insufficiency.

The cases with congenital dilatation of the pulmonary artery may be asymptomatic and discovered only on routine fluoroscopy. Dyspnea is a frequent symptom. Cyanosis is usually present and may be intense. Polycythemia of moderate degree is observed in the cyanotic patients. Cough also is relatively frequent but not severe.

Examination of the Heart

Physical examination of the heart reveals the abnormalities due to the associated cardiac disease as well as those of pulmonary insufficiency. The dilated pulmonary artery causes dullness in the second and third left interspace and occasionally a pulsation in this area. The diagnostic sign is a soft or loud blowing, or harsh diastolic murmur in the second or third left interspace. In cases of mi

tral stenosis this has been termed the Graham Steell[14] murmur (p 660) There is often an associated systolic murmur attributed to eddies in the dilated pulmonary artery The second pulmonic sound may be accentuated, owing to the increased pressure in the pulmonary artery and closer approximation of the dilated artery to the chest wall

Roentgen ray examination discloses evidence of right ventricular hypertrophy (p 105) and of the dilatation of the pulmonary artery [23] The hilar shadows may be prominent and even so large as to be mistaken for mediastinal tumors e g in the cases of congenital or idiopathic dilatation of the pulmonary artery [11] Often there is a distinct pulsation of the pulmonary artery

The electrocardiogram is that observed with right ventricular hypertrophy (p 115)

DIAGNOSIS

The diagnosis depends on the discovery of a pulmonic diastolic murmur and right ventricular hypertrophy and on the absence of left ventricular enlargement or the peripheral circulatory phenomena of aortic insufficiency The diagnosis may be suggested on roentgenologic examination by the finding of a large right ventricle and large pulsating pulmonary arteries

PROGNOSIS AND TREATMENT

These are determined by the underlying or associated disease

PULMONIC STENOSIS

Pulmonic stenosis is almost exclusively a congenital lesion and is discussed in the chapter on congenital heart disease (p 749) Acquired pulmonic stenosis is extremely rare especially as a clinically significant lesion There may be a true stenosis due to inflammation and adhesion of the valves or a functional stenosis incidental to other diseases

Acquired organic stenosis of the pulmonary valve has been attributed to rheumatic valvulitis bacterial endocarditis and to trauma All are very rare Rheumatic inflammation may be engrafted on a congenital bicuspid pulmonic valve [40] In the case of McGuire and McNamara,[29] rheumatic pulmonic stenosis and insufficiency were associated with stenosis of the other three valves The stenotic adherent cusps form a single protruding diaphragm or dome pierced at its center by a small opening There have been a number of reports of right sided valvular lesions including pulmonic stenosis and tricuspid insufficiency in cases of malignant carcinoid of the small intestine with hepatic metastases presumably due to abnormal tryptophan metabolism and excessive serotonin production (p 1042)

Functional pulmonic stenosis results from obstruction of the pulmonary orifice by massive bacterial valvular vegetations and by large emboli extending from the right ventricle into the pulmonary artery I have seen both of these conditions characterized by the sudden development of a loud harsh systolic murmur and a systolic thrill over the pulmonic area Litten [5] has reported pulmonic steno is due to the plugging of the pulmonary artery by echinococcus cysts Pulmonic stenosis may also be caused by the pressure of tumors mediastinal glands or of an aortic aneurysm on the pulmonary artery at or near the level of the valves

There is hypertrophy and dilatation of the right ventricle when the right ventricle fails the right atrium may also become dilated and hypertrophied The left chambers are normal unless there is associated disease of the mitral and aortic valve

A prominent feature is the frequency of pulmonary tuberculosis The pulmonary artery is usually dilated beyond the stenotic site possibly because of atrophy of its wall

CLINICAL FEATURES

The clinical features of congenital pulmonic stenosis are discussed in the chapter on congenital heart disease (p 750) The clinical features of the rare instances of acquired pulmonic stenosis are usually determined by the underlying bacterial endocarditis neoplasm embolism or other causative or associated disease

The *diagnostic signs* due to the pulmonic stenosis per se are the loud rough systolic murmur in the second or third left interspace the palpable thrill in the same area the weak or absent second pulmonic sound the roentgenologic and electrocardiographic evidence of an enlarged right ventricle (coeur en sabot) and prominent pulmonary artery salient

COMBINED VALVULAR DISEASE

For didactic reasons the individual valvular lesions have been described separately. As a rule multiple valves are the site of significant lesions due to rheumatic fever. Mitral stenosis and aortic insufficiency or stenosis occur most commonly. Occasionally organic tricuspid stenosis and insufficiency coexist while significant disease of all four valves is rare. Functional tricuspid insufficiency is not uncommon in the late stages of combined mitral and aortic disease.

The clinical picture including the physical and roentgenologic signs is usually determined by the relative severity of the individual lesions and by their order of development. *As a rule each lesion produces its own* characteristic effects on individual cardiac chambers and its own physical and roentgenologic signs which permit recognition of the multiple lesions. Therefore it is unnecessary to devote separate discussions to the various combinations of valvular lesions.

In some instances one valvular lesion may relieve the strain, or partially neutralize the effects of another. Accordingly, various modifications in prognosis have been attributed to the different combinations of valvular disease. However, such attempted correlations are untenable because other factors, such as rheumatic activity, severity and extent of myocardial damage and the development and severity of complicating coronary atherosclerosis, are extremely important in *determining the course and prognosis* of rheumatic cardiovalvular disease. For *surgical correction* see page 674

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PART VI

ETIOLOGIC FORMS OF HEART DISEASE

Chapter 30

CONGENITAL HEART DISEASE

Despite the epochal contributions of Peacock[311] Rokitansky[335] and Vierordt[405] the subject of congenital heart disease long remained an academic study This was due both to the rarity with which an accurate diagnosis of the lesion could be made and to the inability to remedy the lesion In recent years the scholarly clinical pathologic contributions of Maude Abbott[1] and of Laubry and Pezzi[347] have lent a fruitful stimulus which has resulted in the development of great accuracy in the diagnosis of the exact congenital cardiac lesions or at least of the major defect present in a given case The utilization of contrast media to portray roentgenographically the individual portions of the heart and great vessels (p 11) has enhanced our diagnostic accuracy in this field The employment of intracardiac catheterization (p 74) to determine the oxygen content and pressure within various cardiac chambers and to determine cardiac output and pulmonary blood flow has provided additional diagnostic data The subject of congenital heart disease is now squarely within the domain of the clinical cardiologist great surprises at the pathologist s table should become uncommon At the same time amazing progress has been achieved in the surgical treatment of certain congenital cardiovascular anomalies and these advances enhance the importance of diagnostic accuracy

INCIDENCE

The incidence of congenital cardiac abnormalities is still uncertain and varies in the different age groups According to most reports major congenital cardiac anomalies are found in 0 3 per cent of total births[266] Among adults it is improbable that congenital heart disease forms more than a fraction of 1 per cent of the cases of clinical heart disease On the other hand among school children with cardiac ailments the incidence of congenital heart disease was reported to be 11 per cent and among children above the age of two 14 per cent[44] Below the age of five the vast majority of cases of heart disease are of congenital origin since rheumatic fever is very uncommon in children before this age For this reason the diagnostic importance of determining whether a cardiac lesion was present in infancy or early childhood is obvious

ETIOLOGY

Basic Cause

Congenital anomalies of the heart and great vessels are due to *arrested or defective prenatal development* But it is uncertain whether intrinsic factors in the germ plasm or extrinsic factors in the embryo s environment are of major importance[14] Disease of the fetal envelopes amniotic adhesions or other mechanical disturbances in the environment of the embryo may interfere with that perfection and symmetry of growth which is essential for the normal development of the heart and great vessels That this is the chief causative factor is indicated by the frequent association of other congenital anomalies elsewhere in the body of subjects with cardiac defects and by the occurrence of cardiac anomalies in siblings[6] In some cases the origin of defective development of the heart may be situated in the germ plasm rather than in the environment of the embryo This is indicated by evidence of hereditary factors but *in the great* majority of cases the role of heredity is insignificant

Much of the evidence that disturbances of development (whether due to fetal environment or defective germ plasm) account for congenital cardiac disease is based on a correlation of the lesions observed in human hearts with a phylogenetic study of the structures in the hearts of lower forms including the reptiles amphibians and fishes Notable contri

butions have been made by Rokitansky[335] with respect to septal lesions by Keith[23] on the abnormal development of the bulbus cordis and by Spitzer[375] on the transposition of the great vessels These will be discussed under general embryology and embryology of the individual lesions

Associated Anomalies

The likelihood that congenital cardiac anomalies *are due to disturbances in the* embryo s environment is supported by the frequency of anomalies in other parts of the body in the same subjects, for it is to be anticipated that defects in the localized milieu surrounding the embryo would disturb not only the development of the heart but also that of other structures Vierordt[408] observed *associated anomalies in 80 of 700 cases* (11 per cent) of congenital heart disease Abbott[1] in 188 of 1000 cases (18 8 per cent) Keith[3] found cardiac anomalies in 14 of 23 malformed fetuses

While some of the associated anomalies are of a hereditary nature (see below) others are not and therefore point to the presence of abnormalities *in the fetal environment* Although, on the one hand the occurrence of congenital cardiac disease in identical twins has been used to support a hereditary etiology, in other instances the occurrence of such congenital cardiac malformations in only one of identical twins has refuted the concept of hereditary etiology [18] Mongolian idiocy occurs rather frequently Morse[90] found 6 Mongolian idiots in 100 cases of congenital heart disease and Irvine Jones[18] 7 in her 100 cases Conversely, congenital heart disease was found in 28 (44 per cent) of a series of 63 autopsy cases of Mongolian idiots dying in the first five years of life [149] The cardiac defect most often associated with Mongolian idiocy is either a complete absence of the interatrial septum, a persistent common atrioventricular canal or a persistent ostium primum (p 735 defect in the lower portion of the atrial septum) But in the series studied by Evans,[149] ventricular and atrial septal defects occurred with equal frequency and patent ductus arteriosus and pulmonic stenosis were also associated with mongolism There are often accessory spleens or the spleen is absent

Gargoylism This is associated with some degree of cardiac abnormality in 85 per cent of cases Cardiac enlargement, especially of the right chambers, deformity of the valves subintimal fibrosis *and narrowing of the coronary* arteries, myocardial fibrosis and congestive heart failure have been reported[143] (p 629)

Arachnodactyly or Marfan s Syndrome[79, 230] This hereditary disorder is characterized by congenital subluxation of the lenses, pectus excavatum and pigeon breast dolichocephaly *and highly arched palate long* ' pidery fingers and hyperextensible joints, and a variety of congenital cardiovascular lesions notably (1) medionecrosis of the ascending aorta which may be complicated by *dissecting aneurysm, aneurysm of the sinuses of Valsalva and ascending aorta* and *aortic insufficiency* due to aortic dissection or dilatation, *(2) interatrial septal defect* (patent foramen ovale) and occasionally coarctation of the aorta, subaortic stenosis, pulmonary arterial disturbances, fibromyxomatous endocardial lesions, and others Cardiac murmurs may be due to chest deformities rather than to organic heart disease

Heredity

The possibility that *defects* of the germ plasm account for at least some cases of congenital heart disease is indicated by the following evidences of the role of heredity (1) There are associated anomalies which are generally recognized as being of a hereditary nature These include polydactylism, clubbed foot fetal lobulation of the kidneys and congenital dislocation of the hip (2) There is occasionally an ancestral history of congenital heart disease (3) Cardiac defects have been reported in identical twins (4) There are records of families with multiple instances of similar or identical congenital cardiac anomalies in more than one generation

Virus and Other Infections

The occurrence of rubella (German measles) in the first two or three months of pregnancy has been associated with a significant incidence of congenital cataracts and cardiac anomalies in the offspring [189] This may be related to the fact that the entire development of the heart and great vessels is completed in the first two months of embryonic life At the present time it is recommended that pregnancy be interrupted with the occurrence of rubella in the first trimester of pregnancy

The above observations suggest the possibility that other maternal and fetal infections

may be responsible for congenital heart disease Fetal endomyocarditis and syphilitic myocarditis have been reported as the cause in occasional cases Endometrial bleeding during the first trimester may be a factor in some cases

Nutrition Vitamin Deficiencies Altitude

Animal experiments suggest that dietary deficiencies in the mother may result in congenital malformations [11] But there is no significant evidence of such a relationship between vitamin or other nutritional deficiencies and the occurrence of congenital heart disease in man The determination of certain cardiovascular anomalies has been related to gestation or childbirth at high altitudes [7]

Sex

If all forms of congenital cardiac lesions are considered the incidence of congenital heart disease is almost equally divided between the sexes However certain individual lesions occur with predilection for one sex or the other Thus coarctation of the aorta (3 1) anomalies of the semilunar cusps (5 1) defects of the aortic septum and transposition of the great vessels (2 1 or 3 1) are more frequent among males while patency of the ductus arteriosus (Botalli) occurs more commonly in females (2 or 3 1)

GENERAL EMBRYOLOGY AND PATHOLOGY

In its prenatal development the human heart passes through a series of stages whereby a simple cardiac tube is transformed into four distinct chambers separated by septa and valves and leading into the aorta and pulmonary artery An important effect of this development is the separation of the systemic circulation from that in the lungs The original simple tube is fixed at two points the arterial or cephalic end and the venous or caudal end As the heart grows this tube elongates and since its ends are fixed it bulges and twists in a spiral fashion so as to assume an S shape This so-called torsion is normally clockwise at the arterial and counterclockwise at the venous end By the fourth week (3 mm embryo) the heart is differentiated into a successive series of four chambers which from the venous to the arterial end are (1) the sinus venosus which receives the vitello-umbilical veins (later to become the inferior vena cava) and the ducts of Cuvier (later the superior vena cava and coronary sinus) (2) the atrium (3) the ventricle and (4) the bulbus cordis from which the primitive truncus arteriosus (later the aorta and pulmonary artery) arises

Most of the congenital cardiac disturbances arise between the fifth and eighth weeks of embryonic life During this time the atrium and ventricle are each divided by a septum into two chambers the atrioventricular canal is divided by a septum into left and right segments the atria are separated from the ventricles by valves and the primitive truncus arteriosus is divided into the aorta and pulmonary artery which lead respectively from the left and right ventricles Details concerning the embryologic basis of the various congenital cardiac lesions will be presented in the discussion of the individual anomalies

In most cases of congenital heart disease the lesions are not isolated two or more lesions being present in the same subject The frequency of combined lesions is due in many instances to simultaneous maldevelopment of two different structures in the heart which are in close anatomic juxtaposition Thus proper closure of the upper part of the ventricular septum requires normal development of the aorta and pulmonary artery and the septum between them Hence ventricular septal defects are frequently associated with dextraposition of the aorta and pulmonary stenosis or atresia In other cases a primary lesion produces changes in pressure in the chambers of the heart or great vessels so that fetal openings do not close as they normally should A patent foramen ovale or ductus arteriosus may result secondarily from atresia or stenosis of a valvular orifice or transposition of the great vessels and this patency may be a compensatory lesion to maintain a continuous circulation In other cases a combination of lesions represents simultaneous disturbance in multiple unrelated portions of the heart

GENERAL SYMPTOMATOLOGY

Certain congenital anomalies are of no clinical importance since they produce neither subjective symptoms physical signs nor other objective abnormalities These include bifid apex of the heart persistent left superior vena cava and most instances of patent foramen ovale and of anomalous septa and chordae Other anomalies produce neither symptoms nor signs but are the site of serious

complications e.g., a bicuspid aortic valve is often complicated by bacterial endocarditis In cases of pure dextrocardia with situs inversus there are no symptoms but physical signs and the roentgenoscopic and electrocardiographic examinations reveal a characteristic picture

In another group of lesions there are usually *cardiac murmurs* which may be typical in location and character and associated with palpable *thrills* There are often also *changes in the size and shape of the cardiac silhouette* There may also be *abnormalities in blood pressure* as in cases of coarctation of the aorta or patent ductus arteriosus The latter may be associated with altered circulatory dynamics similar to those in cases of free aortic insufficiency

Symptoms may appear early, as indicated by poor feeding subnormal gain in weight constipation difficulty in swallowing and stridor, syncopal attacks and recurrent respiratory infections Cyanosis may appear with crying and dyspnea with exercise or feeding

Dyspnea on exertion is a common symptom and often appears early in the course of the disease A striking form of dyspnea is that which appears in paroxysms and is usually associated with an intensification of cyanosis In many cases exertional dyspnea is secondary to pulmonary congestion associated with left sided heart failure Dyspnea with signs of pulmonary congestion due to heart failure in infancy is often misinterpreted as pneumonia Often however the dyspnea appears to be due to excessive arterial oxygen unsaturation especially following exercise with consequent anoxia of the carotid sinus and respiratory center *Squatting* especially after exercise is common in certain forms of congenital heart disease with cyanosis and characteristically with the tetralogy of Fallot

Cough complicates dyspnea when the latter is due to pulmonary congestion but both dyspnea and cough may be due to tracheal compression by a double aortic arch or aberrant vessel Congestion of the abdominal viscera with digestive disturbances, hepatic enlargement and ascites and peripheral edema, results from failure of the right side of the heart Excessive fatigability and weakness are relatively common

Cerebral symptoms including faintness dizziness headache are observed occasionally, and more rarely syncope, convulsions, delirium paralyses and coma, especially in patients with cyanosis [3] These symptoms are due partly to cerebral hypoxia (arterial hypoxemia) especially during exertion[213] and partly to the polycythemia with consequent circulatory stasis or complicating cerebral thromboses or hemorrhage Cerebral symptoms may be due to inadequate cerebral blood flow in cases of aortic or subaortic stenosis, to cerebral embolization in complicating bacterial endocarditis or endarteritis, to ruptured congenital aneurysms of the circle of Willis in coarctation of the aorta or to cerebral abscess in cases of septal defects and paradoxical embolism Adams-Stokes attacks may occur in cases of congenital heart block [96]

Cardiac pain was noted in 4 8 per cent of 180 cases of congenital heart disease notably aortic or subaortic stenosis and severe pulmonary stenosis [383] It was related to inadequate coronary perfusion during exercise

Vascular disturbances in the extremities including coldness, numbness and tingling or pain may appear in patients with or without cyanosis and polycythemia These symptoms as well as intermittent claudication are not uncommon in cases with the adult type of coarctation of the aorta Malnutrition and underdevelopment may result from deficient peripheral blood supply

Special symptoms may be identified with individual lesions Thus the pressure of a dilated pulmonary artery a persistent right aortic arch or of an anomalous vessel on the esophagus trachea or recurrent laryngeal nerve may cause dysphagia dyspnea or hoarseness respectively

Sudden death is most likely to occur in cases of idiopathic hypertrophy of the heart subaortic stenosis or Ebstein's disease Otherwise, death in congenital heart disease is due to congestive heart failure anoxia, cerebral complications, vascular thromboses, bacterial endocarditis or some intercurrent illness

The detailed cardiac signs and other features associated with congenital heart disease are best discussed below with the important individual cardiac anomalies

The symptoms often attributed to congenital heart disease are *cyanosis* and *clubbed fingers* But it is erroneous to believe that

these are characteristic of the majority of cases The diagnosis will usually be overlooked if it depends on the discovery of these manifestations since in most cases cyanosis is absent or occurs only as a late or terminal event Cyanosis of varying intensity was encountered in 351 of Abbott s[1] 1000 cases and in 124 others it appeared terminally Since cyanosis is almost always associated with the severe multiple cardiac anomalies which lead to death in infancy or very early childhood this symptom is much less common than indicated by the above figures if only cases above the age of three are considered

The cyanosis is most marked in the lips tips of fingers or toes nose ears conjunctivae and mucous membranes especially of the lips and tongue but it may be generalized In cases of interruption of the aortic isthmus cyanosis is limited to the lower extremities if atresia of the aortic isthmus is combined with transposition of the great vessels there is more intense cyanosis of the head and upper extremities than in the lower In patent ductus arteriosus with reversal of flow (i e flow is from pulmonary artery to aorta) cyanosis is more marked in the lower than in the upper extremities in the left than in the right hand and is especially visible on exercise A distinct cyanosis may be observed in the retina (cyanosis retinae) The optic disc is usually congested The veins are congested purplish red and tortuous Retinal hemorrhages suffusion of the conjunctiva and rarely exophthalmos may be associated Clubbing of the fingers and toes was noted in 132 of Abbott s[1] 1000 cases It usually appears later than cyanosis in any given case time being an important factor in its development

A secondary *polycythemia* occurs frequently in the cases with cyanosis This appears to compensate for the oxygen unsaturation of the blood The red blood count in such cases usually varies between 6 and 7 million per cubic millimeter More marked polycythemia is observed in association with intense persistent cyanosis Occasionally there are 10 to 12 million red blood cells per cubic millimeter The hemoglobin is correspondingly elevated to 110 to 130 per cent in the patient with moderate cyanosis and occasionally reaches 150 to 200 per cent with extreme polycythemia An *increase in blood volume* and *blood viscosity* is associated with polycythemia The *hematocrit* usually exceeds 55 per cent

PATHOGENESIS OF CYANOSIS IN CONGENITAL HEART DISEASE

Cyanosis appears in cases of congenital heart disease when there is more than 5 gm of reduced hemoglobin per 100 cc of blood For pathogenesis see page 204

In the absence of cardiac failure many cases of congenital heart disease never present cyanosis for there is no venous-arterial shunt This group includes the cases of adult coarctation of the aorta pure mitral aortic or subaortic stenosis uncomplicated dextrocardia uncomplicated bicuspid or quadricuspid semilunar valves persistent right aortic arch and many anomalies of the coronary or pulmonary arteries and of the pericardium

In cases with an abnormal communication between the left and right sides of the heart or great vessels cyanosis is absent if the flow is from the left to the right or from the aorta to the pulmonary artery Thus patients with a patent ductus arteriosus (Botalli) a patent foramen ovale or an uncomplicated atrial ventricular or aortic septal defect are usually free from cyanosis because the pressure in the arterial circuit (aorta and left side of the heart) is normally higher than that in the venous circuit and therefore the venous blood does not contaminate the arterial However cyanosis may appear sporadically or terminally (cyanose tardive) in these cases if the pressure on the venous side is elevated sufficiently to reverse the flow through the abnormal communication and thus produce a venous arterial shunt This may result from exercise and in infants from crying or sucking due to an increased venous return to and an elevation of pressure in the right side of the heart Certain pathologic conditions especially pneumonia and other bronchopulmonary disease stenosing or obliterating pulmonary vascular lesions and cardiac failure may also cause cyanosis by elevating the pressure in the right chambers of the heart thus causing a reversal of flow through the arteriovenous shunt

In a third group of cases cyanosis usually is present throughout most of the course of the disease In these cases the flow of blood through the abnormal shunt is constantly from the venous to the arterial side because some associated lesion has caused the pressure on the right or venous side to exceed that on the left side of the heart and aorta In some congenital cardiac lesions such as complete

transposition of the great vessels, extreme dextroposition of the aorta or drainage of the pulmonary veins into the right atrium, there is no actual shunt and there is an adequate pulmonary blood flow, but venous blood is being pumped into the systemic circulation and it is difficult or impossible to direct oxygenated blood to the tissues. Even when the shunt is from the venous to the arterial side, cyanosis develops only if a considerable amount of venous blood is so shunted. This requires either an abnormal communication of large size or a considerably higher pressure on the venous than on the arterial side of the communication.

According to the calculations of Lundsgaard and Van Slyke[265] cyanosis appears in patients with normal hemoglobin if the venous-arterial shunt exceeds 38 per cent of the cardiac output of the heart. Shunts of 40 to 75 per cent of the blood flow in which venous blood bypasses the lungs or mixes freely with arterial blood are common in the tetralogy of Fallot and other congenital lesions, such as tricuspid stenosis, bilocular and trilocular hearts, persistent truncus arteriosus, transposition of the great vessels and combined lesions.

The volume of the shunt can be calculated as the difference between the systemic blood flow and the pulmonary blood flow. Normally, the cardiac output, the systemic blood flow and the pulmonary blood flow are the same and can be calculated as follows:

$$\text{cardiac output (liters per min.)} = \frac{O_2 \text{ consumption (cc./min.)}}{\text{arterial } O_2 \text{ (cc./liter)} - O_2 \text{ of mixed venous blood (cc./liter)}}$$

When there is a right-to-left shunt, the shunt equals systemic blood flow minus pulmonary blood flow.

$$\text{systemic flow} = \frac{O_2 \text{ consumption}}{\text{arterial } O_2 \text{ content} - \text{rt. atrial } O_2 \text{ content}}$$

$$\text{pulmonary flow} = \frac{O_2 \text{ consumption}}{O_2 \text{ content pulmonary vein} - O_2 \text{ content pulm. artery}}$$

O content pulmonary vein is assumed to be 95 per cent of O_2 capacity of systemic arterial blood.

Polycythemia is not usually a factor in the original development of the cyanosis because the latter appears before the former. However, the subsequent development of polycythemia may intensify the degree of cyanosis both because of the increase in the total amount of hemoglobin (and therefore of the concentration of reduced hemoglobin) and because polycythemia leads to engorgement of the subpapillary venous plexus (p. 205) and to peripheral circulatory stasis with increased deoxygenation in the capillaries (p. 205).

The cases of congenital heart disease in which cyanosis appears at birth or shortly thereafter have given rise to the terms "blue baby" and morbus caeruleus. Obviously not all cases of congenital heart disease are blue babies or examples of morbus caeruleus. Furthermore, cyanosis at birth may be due to pulmonary atelectasis or intracranial hemorrhage. In some cases of congenital heart disease cyanosis is absent at birth but appears after weeks or months because a compensating open ductus arteriosus becomes obliterated.

PATHOGENESIS OF CLUBBING IN CONGENITAL HEART DISEASE

Clubbing of the fingers and toes usually occurs only in those cases of congenital heart disease with persistent and longstanding cyanosis. The soft parts of the fingers and toes, especially of the nailbed and sometimes of the nose, increase in size until they present a drumstick or bulbous appearance. The pathogenesis of clubbing whether in cases of congenital heart disease or other conditions is still unclear. In cases of congenital heart disease, clubbing has been attributed to the oxygen unsaturation of the blood with consequent capillary stasis and accumulation of noxious products in the most peripheral parts of the body. On the other hand, clubbing has been viewed as a growth phenomenon which suggests an increased blood flow to the parts affected.[283, 284] The evidence of growth is seen not only in the increased size of the soft part of the fingers and toes but also in the convex forward curvature of the nails, this shape resulting from excessive growth within a confined space.

Direct microscopic study of the capillaries of the nailbed by Redisch and Roesler[illegible] has revealed a sharp increase in their number, marked dilatation of the venous and of the

capillary curve the presence of many fine newly formed capillaries and great dilatation of the subpapillary venous plexus It is likely that these changes in the peripheral venules and capillaries associated with slowing of the circulation as well as the increase in hemoglobin and erythrocyte content of the blood serve to compensate for its oxygen unsaturation But at the same time an excessive supply of other nutriments may be provided which incidentally promotes the proliferation of the soft tissues and thus produces clubbing

COMPLICATIONS

Many of the clinical phenomena in cases of congenital heart disease are not due to the lesions themselves but to the complications to which these lesions predispose These complications are important especially in those subjects who pass adolescence or reach adult life and are apparently asymptomatic or well compensated The chief complications are (1) congestive heart failure (2) subacute (and acute) bacterial endocarditis (3) pulmonary tuberculosis (4) paradoxical embolism (5) cerebral abscess and (6) rupture of the aorta or of a cerebral vessel

Cardiac failure requires no special discussion here

Bacterial endocarditis (p 864)

Pulmonary tuberculosis is more than an occasional complication in cases of congenital heart disease particularly with pulmonary stenosis According to Abbott[1] the incidence of tuberculosis is particularly high in the latter disease (9 of 25 cases or 36 per cent) when the ventricular septum is closed The frequent association of pulmonary tuberculosis with pulmonic stenosis ■ related supposedly to the deficient blood supply to the lungs and ■ contrasted with the relative rarity of tuberculosis in the chronically congested lungs of patients with mitral stenosis (p 665) The association of tuberculosis with pulmonic stenosis has of course become uncommon in areas where the incidence of tuberculosis itself has diminished

Paradoxical embolism (crossed embolism) refers to the passage of ■ portion of thrombus from systemic veins usually in the lower extremities or right side of the heart to the systemic (arterial) circulation In the normal circulation such an embolus would tend to lodge in the pulmonary artery or its branches since it could not traverse the pulmonary capillaries which form the only route to the systemic circulation However in the presence of a cardiac anomaly permitting direct communication between the venous and arterial circulations and notably in the presence of an open foramen ovale a venous thrombus by passing from the right to the left atrium occasionally embolizes a systemic arterial vessel That this is the mechanism of paradoxical embolism is occasionally demonstrable at necropsy in certain cases in which the thrombus is found straddling both sides of an open foramen ovale[102]

In the majority of cases a cerebral artery usually the middle cerebral or one of its branches is the site of embolization But frequently multiple emboli appear the kidney as well as the brain being commonly affected Since the origin of paradoxical emboli is usually in the systemic veins there are often simultaneous uncrossed emboli to the lungs In all six cases of paradoxical emboli reported by Ingham[217] there were also pulmonary emboli Usually the pulmonary embolism precedes the paradoxical embolism In fact the rise of pressure in the right cardiac chambers consequent to pulmonary embolism ■ believed to facilitate the venous to arterial shunt of thrombotic material through a patent foramen ovale or through some other atrial or ventricular septal defect A diagnosis of paradoxical embolism is suggested by occlusion of a systemic artery after pulmonary embolism provided there is no other obvious cause of the systemic embolization such as bacterial endocarditis mitral stenosis with atrial thrombi or myocardial infarction with mural ventricular thrombi

The occurrence of *brain abscess* in cases of congenital heart disease not due to the direct extension of suppuration from neighboring structures was pointed out long ago by Ballet[15] This association has been reviewed by several groups of observers[4, 7, 273, 97] We are not concerned in this discussion with cerebral suppuration secondary to bacterial endocarditis with bacterial embolization of the cerebral arteries As a rule the abscess develops from ■ paradoxical embolism in cases with a patent interventricular septum especially with tetralogy of Fallot and less often with a defect of the interatrial septum Bacterial endocarditis is absent in these cases The abscess is solitary in 90 per cent of the cases Headache and vomiting with or with

out fever, occur early Focal neurologic signs, including hemiplegia and papilledema, are also early manifestations Progression is rapid with early perforation of the ventricular system Meningitis may dominate the clinical picture Early diagnosis, vigorous use of antibiotics aspiration, and drainage or resection of the abscess are important I have twice seen patients with symptoms of a brain tumor who were discovered to have clinical signs of a ventricular septal defect Because of this association a diagnosis of cerebral abscess was made and confirmed by surgical exploration It is presumed though it is usually difficult to prove, that these cases of brain abscess are examples of paradoxical embolism in which the embolic material contains pyogenic organisms Because the abscess is a solitary one, it should be amenable to antibiotic and surgical cure if the diagnosis is made One such cure was reported by Smolik and associates[369]

Spontaneous *rupture of the aorta* in cases of congenital heart disease is usually a complication of coarctation or hypoplasia of the aorta or of medionecrosis of the aorta

Cerebral complications and their symptoms have been discussed (p 730)

THE COMMON TYPES OF CONGENITAL HEART DISEASE

From the practical viewpoint, it is particularly important to be familiar with those congenital cardiovascular lesions which are amenable to surgical treatment Fortunately, the commonest lesions, including those usually free from, as well as those associated with, cyanosis can be alleviated or cured by surgical means The common congenital cardiovascular lesions without cyanosis, which are usually amenable to surgery, are (1) atrial septal defects, (2) ventricular septal defects, (3) pulmonic stenosis, (4) patent ductus arteriosus (5) coarctation of the aorta, (6) double aortic arch and possibly (7) aortic and subaortic stenosis The common congenital lesions associated with cyanosis which are amenable to surgery include (1) tetralogy of Fallot, (2) pulmonic stenosis with interatrial septal defect (3) tricuspid atresia with hypoplastic pulmonary arteries (4) single ventricle with hypoplastic pulmonary artery and (5) pseudotruncus arteriosus with a single vessel supplying both systemic and bronchial arteries The lesions *not* amenable to surgery at present—all associated with cyanosis—are Eisenmenger complex complete transposition of the great vessels truncus arteriosus with the pulmonary artery arising from the common trunk tricuspid atresia with complete transposition of the great vessels transposition of the aorta with overriding pulmonary artery (Taussig Bing), hypoplasia or atresia of the aorta Among the non cyanotic forms of congenital cardiovascular disease not amenable to surgery are idiopathic hypertrophy of the heart, anomalous coronary artery arising from a pulmonary artery, Ebstein s disease and congenital dilatation of the pulmonary artery

ATRIAL SEPTAL DEFECTS

Uncomplicated interatrial septal defect is probably the commonest form of congenital heart disease, occurring in 15 to 20 per cent of cases[4 5] It occurs two to four times as frequently in females as in males

Embryology

About the fourth week of fetal life, a membrane, the *septum primum*, grows downward from the superior posterior wall of the atrium and divides it incompletely into right and left chambers The lower margin of the septum primum has a sickle-shaped defect which is the *ostium primum* Shortly afterward another opening the *ostium secundum*, appears in the upper portion of the septum primum Subsequently a second membrane the *septum secundum*, whose exact origin is uncertain develops slightly to the right of the septum primum and fuses with it It embraces the ostium secundum, leaving an oval opening the foramen ovale which functions as a circulatory pathway in the fetus but usually closes shortly after birth The ostium primum is normally closed during the fifth or sixth week by the downward growth of the septum primum and its fusion with the endocardial cushions which divide the atrioventricular canal into left and right channels Occasionally, however the ostium primum is not

closed and persists in adult life as a defect at the lower end of the interatrial septum An arrest in development of the endocardial cushions with failure to close the gap between the interatrial and interventricular septa results in a common atrioventricular canal the so-called *persistent atrioventricularis communis*

Despite the fusion of the septum secundum and septum primum, the foramen ovale is patent throughout fetal life and for some time after birth During fetal life the mixed blood containing the oxygenated blood from the placenta enters the right atrium and is directed by the sinus valve through the foramen ovale into the left atrium After birth the higher pressure in the left atrium as compared with that in the right causes the valve-like fold about the foramen ovale to occlude the opening But anatomically the foramen is still patent in many individuals until the second year of postnatal life According to Patten[309] functional closure of the foramen ovale occurs in only 35 per cent of subjects by two weeks of age but at six weeks 90 per cent and at three months 98 per cent of individuals have a functionally closed foramen ovale On the other hand complete anatomic closure of the foramen ovale is found in only 18 per cent of subjects at one year in 50 per cent at two years Even among adults 20 to 25 per cent of hearts at necropsy are found to possess an anatomically open foramen ovale In most instances it is only a slit like aperture which just permits a probe to be passed obliquely from the right atrium anteriorly to the left atrium posteriorly (probe-patent foramen ovale)

Pathology

A patent foramen ovale may be of clinical significance only when it is of sufficient size to permit the passage of blood between the two atria In the series of 1100 necropsies studied by Thompson and Evans[40] 6 per cent of the hearts revealed a foramen ovale more than 7 mm in diameter while 29 per cent contained merely a probe-patent opening Usually the atrial septal defect in the adult is large with a diameter of 2 to 3 cm Multiple defects may be present

A knowledge of the variety of atrial septal defects with respect to their size location and complexity of structure is important, not only because they present differences in circulatory disturbance but also because they impose different problems for the surgeon undertaking their closure.[31] There may be only an insignificant probe-patency but with competence of the valve of the foramen in about 25 per cent of cases In cases of valvular incompetent foramen ovale the posterior rim may be complete or incomplete When the rim is incomplete the defect may be continuous with the orifice of the superior vena cava and associated with partial anomalous pulmonary venous drainage especially from the right lung The atrial septal defect may have its lateral margins continuous with the valve of the inferior vena cava to form a false lower margin These defects are generally located high in the septum and there is a rim of septal tissue below them and above the mitral and tricuspid valve rings In another group, the defect is due to a *persistence of ostium primum* and lies on the valve rings In a third group the defect represents an absence in the lower part of the atrial septum and is associated with an opening in the upper part of the ventricular septum perhaps with fusion of the mitral and tricuspid valves or with a single atrioventricular canal

The entire atrial septum may be lacking In such cases if the ventricular septum is present, the subject has a *cor triloculare biventriculare*[113] This condition is rare is usually associated with other lesions and offers a very poor prognosis rarely an individual with this defect lives to the age of 30 with relatively few symptoms There is a striking tendency for Mongolian idiocy to be associated with defects at the lower end of the atrial septum (persistent ostium primum) which are sometimes combined with a common (undivided) atrioventricular canal[332]

Many cases with a significant atrial septal defect are complicated by a valvular lesion this association was encountered in more than three quarters of the 61 cases analyzed by Roesler[331] More recent observations suggest that the incidence of significant associated valvular lesions is much less, probably well below 25 per cent There may be a mitral stenosis less commonly an aortic valvular lesion or both The combination of an atrial septal defect with mitral stenosis is known as Lutembacher s disease[349] According to Nadas and Alimurung[297] Lutembacher s syndrome is rarer than previously thought and occurs in only 6 per cent of all atrial septal defects

When the atrial septal defect is a persistent

ostium primum deformity of the subjacent mitral valve is usual and results in mitral regurgitation [431, 436] Occasionally the tricuspid valve is deformed and incompetent in cases of persistent ostium primum When persistent ostium primum is associated with deformities of the atrioventricular valves the condition resembles or may be identical with a partial common atrioventricular canal In the latter however a defect in the ventricular septum should be demonstrable

Atrial septal defects are common in association with a variety of congenital cardiovascular lesions associated with cyanosis serving as the sole or major route for blood from the right side of the circulation to reach the left The most common associated congenital lesions include tricuspid atresia pulmonic stenosis transposition of the great vessels Eisenmenger s syndrome and Ebstein s disease

The heart is very large and averages 550 to 600 gm in weight But there may be no significant enlargement of the heart with small septal defects The enlargement involves particularly the right ventricle and right atrium which are exceedingly dilated and hypertrophied Almost the entire anterior aspect of the heart in situ is formed by the dilated right chambers, while the left ventricle appears as a small appendage which is just visible near the apex Even with associated mitral stenosis the left atrium is usually of normal size or only slightly enlarged because the flow of blood has free egress through the septal defect and because the mitral stenosis is not severe But in persistent ostium primum with mitral regurgitation, the left ventricle may be enlarged and hypertrophied

The pulmonary artery, whose diameter is normally less than that of the aorta is relatively larger in this disease Occasionally the pulmonary artery and its branches are greatly dilated and may reach aneurysmal proportions This exaggerated pulmonary dilatation is an essential feature of the disease as described by Lutembacher [267] There may be pulmonary arteriolar sclerosis and narrowing, or, occasionally gross thrombosis of the main pulmonary arteries [88] The aorta is hypoplastic

Pathologic Physiology

In uncomplicated atrial septal defect, the shunt is from left to right since the left atrial pressure exceeds that within the right atrium [72, 80] However, right to left shunts of small magnitude may occur intermittently with changes in pressure relationships [339, 356] That such right to-left shunts occur is indicated by an average arterial oxygen saturation of 85 per cent in a group of patients with atrial septal defect whose pulmonary artery and right ventricular pressure were normal [48] When pulmonary arterial hypertension was associated with atrial septal defect, the average oxygen saturation was 71 per cent and, [illegible] course most of the patients in this group were cyanotic

The *pulmonary blood flow*, i e, the right ventricular minute output, is strikingly increased to between 7 and 22 liters per minute,[189] instead of a normal of about liters This is the result of the increased blood flow into the right ventricle from the right atrium, which receives blood both from the vena caval systems and from the left atrium The work of the right ventricle is thus increased and this chamber becomes enlarged and hypertrophied The systemic blood flow is normal or slightly decreased, hence the pulmonic blood flow ranges from somewhat greater than, to more than four times the systemic blood flow according to the varying magnitude of the shunt

The *pulmonary artery blood pressure* may be normal or elevated usually without relation to pulmonary blood flow Blount et al [48] found the pulmonary blood flow averaged 13 2 liters in a group with normal pulmonary blood pressure and 8 0 liters in a group with elevated pulmonary blood pressure Occasionally the pulmonary blood pressure is equal to the systemic blood pressure Although the pulmonary artery pressure may rise because of very increased blood flow (e g when three or more times normal), the major cause for the pulmonary hypertension is an increase in pulmonary arteriolar resistance which averages 122 dynes/second/cm^{-5} in tho e with relatively normal pulmonary arterial pre ures and 770 in those with pulmonary hypertension It appears that the pulmonary arteriolar resistance is a major factor in determining the magnitude of the shunt and of the increased pulmonary blood flow [115] The pulmonary flow is large and the associated pulmonary artery pressure [illegible] normal in one group of cases because the pulmonary resistance is small and presumably therefore the pulmonary vascular bed distensible In the

and associated with a thrill, and the second sound is widely split

With the development of congestive heart failure the cervical veins become full In the presence of atrial fibrillation which occurs frequently there may be a systolic pulse in the liver and cervical veins (pp 72) with regular sinus rhythm there is a presystolic venous and hepatic wave (double pulse wave p 715)[171] just as in cases of tricuspid stenosis The radial pulse is often small

Roentgenology[303]

The essential features are

1 A prominent main pulmonary artery (Fig 129)

2 A small aortic knob or absence of the aortic knob

3 Prominent hilar shadows and large sharply defined branches of the pulmonary artery These are not invariable findings increased pulmonary vascular markings are almost always present in the acyanotic cases absent in the cyanotic[106] The hilar vessels may clearly pulsate (hilum dance) The larger hilar vessels may be mistaken for a mediastinal tumor or lymphoma and needless surgery or radiotherapy undertaken There is increased pulmonary vascularity The left atrium is usually of normal size but may be slightly enlarged The barium filled esophagus may be displaced as in uncomplicated acquired mitral stenosis

4 There is often a prominent right atrial shadow in the posteroanterior and left anterior oblique views and there may be evidence of right ventricular enlargement Sometimes there is a large globular cardiac shadow without striking enlargement of the pulmonary artery or hilar vessels When there is a persistent ostium primum with mitral regurgitation the left ventricle may be enlarged as well as the right

Pulmonic stenosis may be associated with a prominent pulmonary artery due to post stenotic dilatation but the pulmonary fields are clear A high interventricular septal defect may also be accompanied by a prominent pulmonary artery but the left as well as right ventricle is enlarged Patent ductus arteriosus may be differentiated as it is usually associated with a normal or large aortic knob

Angiocardiography

Atrial septal defects may be demonstrated angiocardiographically by means of a special technique involving synchronous radiography in two planes at right angles (right and left anterior oblique) at the rate of 10 to 12 exposures per second in each plane with precise timing of the exposures on a simultaneously recorded electrocardiogram[60] If the defect is not large its demonstration requires that the contrast medium be injected from below to reach the inferior vena cava whence it is most likely to pass through the defect into the left atrium

The speed of exposures yields films demonstrating the actual passage of the contrast substance through the septal defect immediately after it reaches the right atrium If the shunt is from left to right the contrast material is shunted into the left atrium chiefly during diastole If the shunt is demonstrated in atrial systole it indicates a right-to left shunt By this technique Lind and Wegelius[261] demonstrated atrial septal defects in 30 (20%) of 150 infants believed to have congenital heart disease This is the most direct method of demonstrating the septal defect by angiocardiography But even by conventional angiocardiography the presence of an interatrial septal defect may be indicated by the early opacification of the left atrium by maintained opacification of the right heart or occasionally by actual reopacification of the right heart

Electrocardiogram

There is usually a right axis deviation and almost always evidence of right ventricular hypertrophy or more commonly of incomplete right bundle branch block as revealed by the precordial leads[30, 370] The electrocardiographic pattern is that attributed to diastolic overloading of the right ventricle[70] The typical rSr pattern seen in cases of atrial septal defect has been attributed to hypertrophy of the crista supraventricularis and not to right bundle branch block[47] In the ostium primum defect there is more likely to be a left axis deviation in extremity leads and signs of right ventricular hypertrophy in the precordial leads The QRS complexes may be of high voltage notched and frequently widened[7] High P waves are often present especially in V_1 The P R interval is sometimes prolonged Atrial fibrillation is common toward the end of the disease Incomplete right bundle branch block in a case of congenital heart disease should suggest the presence of an interatrial septal defect

group of cases with increased pulmonary resistance distensibility is limited increased pulmonary blood flows are more difficult to accommodate and then only by a rise in pulmonary blood pressure The cause of the increased pulmonary arteriolar resistance is uncertain but in some cases examined at autopsy there were associated anatomic lesions with narrowing of the small pulmonary arteries and arterioles or occasionally with thrombosis of the major pulmonary arteries [88]

Clinical Features

There may be no significant symptoms and no interference with a normal or even a long life span When symptoms are present, the most common are exertional dyspnea palpitation fatigability or weakness In infants and children there may be feeding difficulties recurrent respiratory infections and retardation of growth [1?] Often symptoms are precipitated by an upper respiratory infection Recurrent attacks of pneumonia pulmonary infarction and pulmonary congestion (left sided heart failure) are characteristic in some cases Cyanosis is usually absent throughout most or all of the course of the disease because the shunt of blood is from the arterial to the venous side of the heart but cyanosis was encountered in 7 per cent of 180 proven autopsy cases [89] Late or terminal cyanosis (cyanose tardive) may appear with a reversal of the shunt if the pressure in the right atrium is made to exceed that in the left because of pulmonary complications pulmonary vascular disease or heart failure Clubbing is absent except in rare instances in which there is persistent cyanosis [359]

The patients are sometimes underdeveloped slender or even infantile (habitus gracilis) The skin may be semitranslucent the bony structure light, puberty delayed and menstruation abnormal Arachnodactyly may be a significant association (p 728) The underdevelopment is attributed to the diminished blood flow through the aorta into the systemic circulation

Eventually the clinical course is terminated most often by symptoms of right-sided congestive heart failure with evidences of venous engorgement, subcutaneous edema ascites and hydrothorax Dexter also noted left ventricular failure in 14 of 60 cases of atrial septal defect [116] Subacute bacterial endocarditis is a rare complication [43] The occurrence of paradoxical embolism has been mentioned Furthermore an atrial septal defect represents the only congenital cardiac anomaly which is frequently associated with paroxysmal tachycardia and atrial fibrillation Extrasystoles atrial flutter ventricular escape and atrioventricular dissociation also have been noted

Hoarseness may result from paralysis of the left recurrent laryngeal nerve due to giant dilatation of the pulmonary artery [417]

In cases of ostium primum the clinical picture is similar to that of other atrial septal defects but the symptoms tend to occur earlier and to be more incapacitating

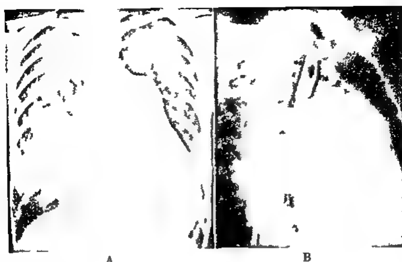
Physical Examination

There may be a left-sided deformity of the chest due to forward pressure of the right ventricle against the precordium Palpation and percussion reveal enlargement of the heart the apex being displaced downward and to the left while the right border is extended to the right of the sternum

A systolic murmur is present in most cases but its location is variable Most often there is a loud systolic murmur only occasionally accompanied by a thrill, in the second or third interspace near the left border of the sternum But it may also be heard lower near the sternum or at the apex It is thought to be due to increased blood flow through the pulmonary valve orifice (relative pulmonic stenosis) In about one third of the cases there is an apical diastolic murmur not due to an associated mitral stenosis, since it disappears after surgical closure of the septal defect, but possibly due to a functional (relative) tricuspid stenosis caused by the large blood flow through the tricuspid orifice In advanced cases there may be a diastolic murmur of pulmonic insufficiency The second pulmonic sound often is accentuated but wide splitting of the second sound is more diagnostic according to Barber et al [20] and Leatham and Gray [474]

In cases of ostium primum which are associated with mitral valvular incompetence there is a loud, high pitched blowing murmur over the apical and lower left sternal regions A low pitched diastolic rumble in the tricuspid region is usual in these cases, probably because of the very marked increase in blood flow with consequent functional tricuspid stenosis

When pulmonic stenosis is associated with interatrial septal defect the systolic murmur in the second and third interspace is very loud



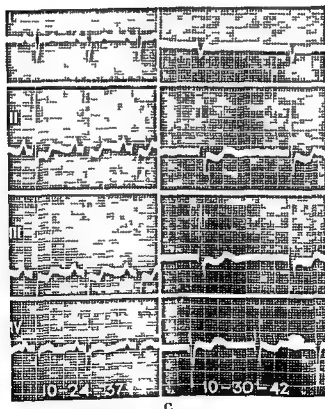


Fig. 129 Interatrial septal defect. *A* Posteroanterior view. Huge pulmonary artery and branches.
B Right oblique view. Rounding and compression of esophagus by large left atrium due to associated mitral stenosis.
C Electrocardiogram of same case 10/24/37. Pronounced right ventricular strain. 10/30/42 developed atrial fibrillation. This arrhythmia in congenital heart disease suggests interatrial septal defect.

Cardiac Catheterization and Diagnosis

The diagnosis is based on the finding of a loud systolic murmur in association with pronounced globular enlargement of the cardiac silhouette especially the right chambers, with small aortic knob and prominent pulmonary artery and branches Confirmation may be presented by intracardiac catheterization, which reveals a distinctly higher oxygen concentration in the right atrium than in the superior vena cava [3,7] This sharp rise in oxygen content may be missed if the catheter is too near the coronary sinus On the other hand, similar oxygen findings occur with partial transposition of the pulmonary veins into the right atrium Occasionally the catheter slips through the interatrial opening into the left atrium and arterial blood is obtained This gives a more positive diagnosis of interatrial defect than the oxygen findings In cases of ostium primum the catheter crosses over in a low position into the left atrium and readily enters the left ventricle The differential diagnosis of this and other congenital lesions is discussed in more detail at the end of the chapter (p 793)

Prognosis

The prognosis is relatively favorable as compared with that in other congenital cardiac lesions The average age at death is about 35 but half the patients live beyond the age of 50 The disease may be extremely well tolerated as in Firket's[156] patient, who lived to be 74 and had eleven pregnancies, Lutembacher's [67] patient who survived seven pregnancies and died at the age of 61 and a patient who survived to the age of 82 [14]

Surgical Treatment

Atrial septal defects may be corrected by atrioseptopexy the use of an atrial well, or under direct vision using hypothermia with inflow stasis cross circulation or an 'artificial heart' (pump oxygenator)

Patients are considered for these operations if they have significant disability due to exertional dyspnea or recurrent episodes of heart failure There should be evidence of right ventricular hypertrophy and catheterization studies should show pulmonary blood flows at least twice the systemic blood flow With even larger pulmonary blood flows operation is probably indicated even in asymptomatic patients An elevated pulmonary artery pressure is not always a contraindication, but suggests care in excluding associated anomalies The combination of pulmonary hypertension and a large left to right interatrial shunt is regarded as a strong operative indication But pulmonary hypertension with a right-to left interatrial shunt is generally a contraindication

In Bailey's technique of atrioseptopexy,[11] the left index finger is inserted through an opening in the right atrial appendage and the defect outlined by touch A portion of the lateral wall of the usually large redundant right atrium is sutured down to occlude the defect completely Associated anomalies of the pulmonary veins and significant mitral stenosis are corrected at the same time This technique limits repair generally to defects with complete rims in the middle of the septum It cannot be used in children below the age of four because the appendage is too small to admit the finger Among 50 patients operated on by Bailey's group there were 5 deaths (13 5%) in 37 patients with persistent ostium secundum and 8 deaths (61 5%) in 13 patients with persistent ostium primum [119]

Another "closed" method used by Crafoord[18] involves similar insertion of the finger in the right atrial appendage following a dissection in the groove between the right and left atrial walls With the finger as a guide a needle and suture are passed through the right atrial wall, then subendocardially in the rim of the defect through the upper portion of the interventricular septum and out again through the atrial wall The septal rim is thus drawn down to the ventricular septum and the defect closed The two ends of the suture are drawn taut over a piece of Fibrin Foam in the groove previously dissected between the superior vena cava and right pulmonary veins This technique was used in 12 patients with survival in 10, and is said to be applicable to all types of septal defects including those associated with a common atrioventricular canal [103]

The atrial well technique of Gross[242, 412] allows more freedom of exploration and repair The right atrium is approached by a right anterolateral thoracotomy through the fifth interspace the incision curving around under the right breast A large rubber well (truncated cone) about 15 cm tall, 13 cm in diameter at the top and 4 cm at bottom, is sutured onto an incision in the right atrium A clamp on the atrium is released and the blood

in that chamber rises into the well to a height equal to the intra atrial pressure This loss of blood is compensated by a slow transfusion of 300 to 500 cc blood given prior to opening the well As the blood is kept fluid by heparin dripped into it the surgeon is able to explore the defect and repair it with his hand beneath the surface of the blood Small defects are repaired by direct sutures and approximation of the septal margins Larger defects are closed by a piece of polyvinyl (Ivalon) sponge or other plastic cut to the proper shape and size placed on the left side of the septal remnant and secured in place by interrupted mattress sutures Eventually the atrial clamp is reapplied the atrial well cut away the right atrial incision sutured and the clamp removed Kirklin and associates [illegible] reported 33 such operations with only one death and an excellent result in 29[84a] Muller and associates[93] used the technique of atriopexy or the atrial well in 18 patients in 14 of whom a successful closure and good clinical result were obtained The operation is contraindicated in patients with pulmonary hypertension and an elevated right atrial pressure

Operation under direct vision in a dry field is possible by refrigeration of the anesthetized patient whose rectal temperature is reduced to 28 C, and by occluding the body inflow fo up to 15 minutes[282, 285] (See Hypothermia p 1112) During this period the right atrium is opened and the defect closed Lewis et al[281] reported operation with this procedure on 31 patients 4 of whom died Postoperative physiologic studies[43] of patients operated on by the technique of hypothermia and direct vision have shown a marked reduction of pulmonary blood flows to levels equaling systemic blood flow Clinical symptoms such as dyspnea and fatigability were greatly ameliorated The pulmonic systolic murmur disappeared in some diminished in intensity but persisted in others Its persistence despite closure of the septal defect suggested that the murmur was not due to the septal defect but to some other factor possibly a functional pulmonic stenosis The apical diastolic murmur disappeared in all cases indicating that it was not due to mitral stenosis but to a functional tricuspid stenosis caused by the immense preoperative pulmonary blood flow Reduplication of the second pulmonic sound and the bundle branch block pattern in the electrocardiogram persisted An extracorporeal pump-oxygenator circuit has been used to repair experimental interatrial septal defects[35] and more recently clinical atrial septal defects in humans[132, 257] (pp 1114 1115)

Operation under direct vision would appear to be more desirable than the closed methods, especially for complex defects and those low in the septum involving the atrioventricular valve or associated with interventricular septal lesions or persistent atrioventricularis communis One would also be more certain of an accurate and complete repair under direct vision and of finding and repairing associated anomalous veins or multiple defects Two factors militate against the general acceptance of the open procedures at present (1) Excellent results have been obtained without direct vision using the well technique sometimes even in cases of the more complex defects (2) Hypothermia is still associated with some serious risk especially of ventricular fibrillation and imposes limitations on the time permitted for repair Extracorporeal pump oxygenator techniques still suffer from technical and physiologic difficulties which, however should be overcome shortly Regardless of the type of procedure there still appears to be difficulty in obtaining consistently satisfactory results or avoiding complications or fatalities in the cases of ostium primum and related complex lesions

PERSISTENT ATRIOVENTRICULARIS COMMUNIS

There is an arrest of development of the ventral and dorsal endocardial cushions and the atrial and ventricular septa fail to meet resulting in low atrial and high ventricular septal defects and a more or less common atrioventricular canal The atrioventricular cusps are deformed and incompetent The shunt is predominantly from left to right and there is usually no cyanosis There is an apical systolic murmur The right atrium right ventricle and to a lesser extent the left ventricle are enlarged Angiocardiography shows early filling of all four chambers There is continuous opacification of both sides of the heart Heart failure often develops at an early age Most of these patients succumb in the first year of life but some reach adult life Mongolism may be associated

COR TRIATRIUM[305, 315]

A transverse septum with a single small opening runs across the left atrium separating

the openings of the pulmonary veins from the mitral orifice There may be stenosis of the common pulmonary vein causing obstruction resembling that of mitral stenosis The clinical picture is characterized by progressive pulmonary congestion with respiratory distress, progressive cardiac enlargement and signs of congestive heart failure Roentgenographic examination shows enlargement of the middle left cardiac salient and of the right ventricle and the electrocardiogram reveals right ventricular hypertrophy The course depends in part on the size of the opening in the transverse septum A triatrial heart was repaired by open cardiotomy in a 29 year old man, with the aid of hypothermia and venous inflow occlusion [25,8] The third atrial chamber was opened while a finger in the left atrium invaginated the abnormal septum into the third chamber The septum was then divided under direct vision

ANOMALOUS ENTRANCE OF THE PULMONARY VEINS[371, 06, 186, 10, 416, 91, 92, 184]

This is discussed here because of its common association with atrial septal defects and because surgical treatment is undertaken at the same time as that for the atrial defect It is one of the more frequent congenital cardiovascular anomalies There may be *total anomalous pulmonary venous drainage*,[395] all the veins draining into the left innominate vein the right atrium the superior vena cava, or a persistent left superior vena cava,[416] or *partial anomalous venous drainage*, in which one or more pulmonary veins drain into the right atrium or superior vena cava, or more rarely into the coronary sinus, left innominate vein vena azygos portal vein persistent left superior vena cava [187] or other veins From the viewpoint of surgical correction in cases of total anomalous pulmonary venous drainage, it is important to know that the pulmonary veins from both lungs usually converge to form a chamber or sinus from which a single anomalous vein emerges to join the systemic venous circulation [63]

There is usually an atrial septal defect or occasionally a common atrial chamber or a patent ductus in the total form life being thus maintained by a right to-left shunt Actually there is first a left to right shunt at the level of the superior vena cava or right atrium, the blood in the right atrium thus receiving oxygenated as well as unoxygenated blood then there is a right to left shunt through the atrial septal defect (or patent ductus) whereby this unoxygenated as well as oxygenated blood reaches the systemic arteries Hence the diagnostic feature which distinguishes total from partial pulmonary anomalous venous drainage or uncomplicated atrial septal defect, is that the right atrial blood is not only significantly more oxygenated than that in the inferior vena cava but also the right atrial oxygen saturation is equal to that of systemic arterial blood The latter is subnormal in oxygen saturation Since a functionally common atrium without pulmonary venous connection could produce the same findings, it is preferable to study the blood in the right ventricle as well as the right atrium In total anomalous pulmonary drainage the right ventricular oxygen saturation equals that in a peripheral artery

An atrial septal defect is also found commonly in cases of partial anomalous pulmonary venous drainage but in such cases of combined interatrial septal defect and anomalous venous drainage, the shunt is from left to right except where most of the pulmonary venous blood drains into the right atrium

Total anomalous pulmonary venous drainage [34, 287, 367] is characterized by slight cyanosis, increasing dyspnea and fatigue, progressive enlargement of the right cardiac chambers and pulmonary artery, increased right atrial pressure, high oxygen saturation of the blood in the right atrium and identical but subnormal oxygen saturation of the peripheral arterial blood and of that in the right ventricle or pulmonary artery There are signs of chronic pulmonary congestion repeated pulmonary infections and eventual right sided heart failure Death occurs usually in infancy or early childhood, but patients have survived into young adult life

Partial anomalous pulmonary drainage is now being commonly diagnosed by cardiac catheterization angiocardiography, selective angiocardiography,[11] dye dilution curves (p 798), or by careful exploration during operations for atrial septal defects The condition is usually benign and may remain asymptomatic, depending on the quantity of anomalous drainage When a large proportion of the pulmonary venous blood drains into the right superior vena cava or right atrium, the clinical picture resembles that described for uncomplicated atrial septal defect There is an

increase in pulmonary blood flow, enlargement of the right cardiac chambers and pulmonary artery, accentuated second pulmonic sound and occasional systolic murmur. The electrocardiogram shows right ventricular hypertrophy or bundle branch block.

On roentgenographic examination[65] the anomalous veins produce a crescentic saber-shaped shadow of vascular density parallel to or behind the right side of the heart, directed into the right atrium or inferior vena cava. Tomography may show the vessels more clearly. The main pulmonary arteries are large and pulsate vigorously, and the right cardiac chambers are enlarged. The pulmonary fields are greatly engorged. The heart is often shifted to the right. There is a diminution in size of one hemithorax due to hypogenesis or agenesis of the lung or bronchi on the side of the involved veins. When all the pulmonary veins empty into the right side of the heart, their shadows form a typical figure of 8 pattern.[34, 380] The anomalous veins often enter a persistent left superior vena cava, which appears as a distinctive wide mediastinal shadow enveloping the aortic knob and pulmonary arc.

Angiocardiographic study has frequently disclosed a constant filling defect at the site of insertion of the anomalous pulmonary veins, thought to be due to turbulent inflow of blood impinging against the contrast material.[380]

A diagnosis of partial anomalous pulmonary circulation may be made if the catheter passes directly into the pulmonary vein before entering the right atrium (i.e., the catheter reaches the pulmonary field without traversing the cardiac shadow) and if a sample of arterialized blood is obtained. But if the anomalous vein empties into the right atrium directly, it may be difficult to distinguish the findings from those of an atrial septal defect. Diagnosis may be aided by the differences in time-dilution curves of Evans blue (T 1824) during its initial circulation after injection into the right and left pulmonary arteries, or by the differences in the curves after injection of the dye into the pulmonary vein and the venae cavae.[387]

Partial anomalous pulmonary venous drainage is associated with a high incidence of pulmonary disease. If a lobectomy or pneumonectomy is to be performed, it is important to be certain that the remaining pulmonary veins drain into the left atrium.

Surgical Treatment

Because of the unfavorable outlook for anomalous pulmonary venous drainage, surgical treatment should be considered if studies indicate the presence of a vessel which is suitable for transplantation into the left atrium.[10-34] Complete correction of the anomaly requires operation under direct vision with the aid of hypothermia, cross circulation, or a pump-oxygenator heart-lung by-pass. Operation is indicated in cases of partial anomalous drainage only if there are disabling symptoms or evidence of considerable enlargement of the heart or a large left-to-right shunt and excessive pulmonary blood flow, as in atrial septal defect. During operations to repair an interatrial septal defect, consideration should be given to the simultaneous implantation of the anomalous veins into the left atrium.[172] If the septal defect is closed by a plastic prosthesis with the aid of an atrial well, the prosthesis can be so placed that the anomalous pulmonary veins are to its left and now enter the left atrium. In the procedure of atrioseptopexy (p. 740) the right atrial wall with the anomalous pulmonary veins can be invaginated through the atrial septal defect, thereby closing the defect and causing the veins to drain into the left atrium. A case of anomalous pulmonary venous drainage into the left innominate vein in association with mitral stenosis was reported.[381] Mitral commissurotomy and transplantation of the anomalous vein into the left atrial appendage were successfully performed at one operation.

In 10 cases in which an atrial septal defect was repaired by atrioseptopexy, the procedure was modified to correct simultaneously partial anomalous pulmonary venous drainage into the right atrium and/or superior vena cava. Lewis et al[15-a] repaired the total anomalous pulmonary venous drainage entering the right atrium by open cardiotomy with the aid of hypothermia and venous inflow occlusion. Burroughs and Kirklin[164] reported 3 cases of total anomalous pulmonary venous drainage in which corrective operations were performed, in 1 with the atrial well technique and in 2 with the aid of an extracorporeal circulation.

LEFT SIDED SUPERIOR VENA CAVA[77, 380]

Persistence of the fetal left superior vena cava is now commonly recognized, especially by cardiac catheterization or angiocardiography. It may appear as an isolated anom

aly but is also likely to occur in the presence of some degree of transposition of the viscera or in association with atrial or ventricular septal defect tetralogy of Fallot, mitral atresia or Taussig Bing heart As a rule, there is a superior vena cava on the right as well as the left side the latter draining into the right atrium by way of the coronary sinus In the less common type the left superior vena cava drains into the left side of a single atrium and the right superior vena cava into the right side of this chamber In this type there may be no inferior vena cava Occasionally a left superior vena cava empties into the left atrium and then other malformations are associated Persistence of the left superior vena cava is due to failure of the upper part of the left anterior cardinal vein to become obliterated The persistent left superior vena cava may be seen in the conventional posteroanterior roentgenogram as a para mediastinal bulge below the aortic arch[303] The vessel is visualized by angiocardiograms if the contrast material is injected in the left arm

Rarely the inferior vena cava opens into the left atrium[186]

Prenatal closure of the interatrial foramen[88] results in atrophy of the left atrium and ventricle After birth the atrophic left atrium cannot accommodate to the large pulmonary venous return with resulting pulmonary congestion dyspnea cyanosis and occasional generalized edema A similar disturbance and clinical picture may arise in cases of aortic atresia congenital mitral stenosis or hypoplasia of the left ventricle[201]

VENTRICULAR SEPTAL DEFECTS

Defects of the interventricular septum have been regarded as the second most frequent cardiac anomaly but this is probable only if all cases with associated lesions are included Only 6 per cent of Abbott s congenital cardiac cases were of uncomplicated ventricular septal defect In a recent series of 750 cases of congenital heart disease isolated ventricular septal defects occurred in 8 per cent[45] Ventricular septal defect also occurred as part of the tetralogy of Fallot in 11 per cent as part of the Eisenmenger complex in another 2 5 per cent, with pulmonic stenosis and a normal aortic root in 2 per cent with pulmonary atresia in 1 5 per cent and transposition of the great vessels in 1 per cent However since more recent studies with cardiac catheterization and other diagnostic techniques, it appears probable that many cases of so-called ventricular septal defect have been incorrectly diagnosed[45]

The cases of uncomplicated ventricular septal defect are known as Roger s disease, Roger[32] described the characteristic murmur associated with this lesion According to Wood et al[45] the term, Roger s disease, if used at all should be applied only to the mild asymptomatic cases characterized solely by Roger's murmur and thrill On the other hand there are also uncomplicated ventricular septal lesions of moderate and great severity with significant circulatory disturbances and clinical symptoms

Embryology

During the second month of fetal life the ventricle is divided into two chambers by a septum which grows upward along the anterior and posterior margins The posterior margin is completed above by joining the posterior endocardial cushion of the atrioventricular canal The anterior margin is incomplete above leaving an interventricular foramen Normally this foramen is closed at about the eighth week by a downward extension of the proximal end of the septum of the bulbus arteriosus The bulbar septum fuses with the incompleted upper end of the interventricular septum and with the posterior endocardial cushion The major primary portion of the interventricular septum is a muscular structure The later segment which closes the interventricular foramen is thin and membranous (septum membranaceum) and is situated in the so-called undefended space of Peacock

Pathology and Pathologic Physiology

A ventricular septal defect usually results from failure of the bulbar septum to close completely the interventricular foramen This deficiency of the bulbar septum may be associated also with some abnormality in the division of the truncus arteriosus into aorta and pulmonary artery and in the position of these great vessels (see below, p 755) For this reason a defect in the ventricular membranous septum is often combined with a dextraposition of the aorta and stenosis of the pulmonary artery The juxtaposition of the septal leaflet of the tricuspid valve to the fetal interventricular foramen accounts for relatively frequent associated anomalies of that

valve including fenestration of the valve with consequent tricuspid regurgitation In such cases of defective tricuspid septal leaflet and high ventricular septal defect there is a virtual direct shunt from the left ventricle to the right atrium[376] If the disturbances in growth are only slight the ventricular septal defect may appear as an isolated lesion Sometimes ventricular septal defects are classified into two types (1) the type in the septum proper responsible for so-called Roger s disease and (2) high ventricular septal defects in the membranous portion of the septum immediately below the aortic valve (p 747) due to failure of the aortic and ventricular septa to meet Often there are associated anomalies such as transposition of the great vessels atrial septal defects[170] or pulmonic stenosis

The uncomplicated ventricular septal defect may be so small as to permit only the entrance of a probe or it may be large enough to admit the thumb It is situated usually in the upper part of the septum just anterior to the septum membranaceum[367] Its margins may be thickened owing to the tension of the blood stream Similar sclerosis may appear on the endocardium of the right ventricle opposite the septal defect Both of these sites may become infected with bacterial vegetations The heart itself is only slightly enlarged the enlargement involving chiefly the right ventricle in cases of small defects But with large (high) interventricular septal defects the left ventricle is more dilated and hypertrophied than the right However the right ventricle is hypertrophied when there is associated pulmonary hypertension The pulmonary artery is dilated in large high ventricular septal defects

The flow of blood through the interventricular opening is from the left to the right ventricle owing to the higher pressure in the former Hence the systemic blood is not contaminated by unoxygenated blood and there is no cyanosis In mild cases the left-to-right shunt is small and the pulmonary blood flow may be only slightly more than the systemic flow In severe cases the pulmonary blood flow may be three to five times that through the systemic circulation[4,5] In such cases there is a high pulmonary vascular resistance and pulmonary hypertension This may represent a persistence of the high pulmonary resistance in the fetus and usually there are pulmonary vascular obliterative lesions in the small arteries and arterioles[37] When the pulmonary hypertension is very marked i e the pulmonary artery pressure is equal to or slightly greater than the systemic there is a bidirectional or reversed shunt[35] These latter cases represent the Eisenmenger complex[47] although to be accurate the Eisenmenger complex includes an overriding aorta There is some evidence that bidirectional shunting or a right-to-left shunt in isolated ventricular septal defect occurs only if there is an associated overriding of the aorta[50] Lesser degrees of pulmonary hypertension not sufficient to cause a right to-left shunt may occur as a result of increased pulmonary blood flow without markedly increased pulmonary resistance Usually the pulmonary blood flow must be at least three times normal to produce so-called hyperkinetic hypertension When there is marked pulmonary hypertension due to increased pulmonary resistance but the right ventricular pressure is slightly less than the left ventricular pressure throughout the cardiac cycle there may be only a small left to-right shunt

When a ventricular septal defect is associated with pulmonic stenosis and overriding aorta (tetralogy of Fallot) the shunt is almost always from right to-left However there are cases of ventricular septal defect with pulmonic stenosis in which there is a left to-right shunt through the septal defect and an increased pulmonary blood flow despite the pulmonic stenosis[10, 11]

Clinical Features

Only the mild cases with small shunts are associated with the classic picture of Roger s disease and are characterized as asymptomatic acyanotic and having a very favorable prognosis On the other hand in patients with large ventricular septal defects and large shunts there may be evidence of underdevelopment recurrent pulmonary infections and early congestive heart failure with death due directly to the septal defect[71] Cyanosis may be present in patients with marked pulmonary hypertension and intermittent or continuous reversal of the shunt usually associated with overriding aorta (Eisenmenger complex) It may also occur in some patients only during exercise pulmonary infections or the development of heart failure Although the muscular defects in the ventricular septum are usually small and asymptomatic they

may be rarely associated with pulmonary hypertension and severe symptoms [99]

The characteristic *physical sign* in cases with a small ventricular septal lesion is a distinctive prolonged usually loud and harsh systolic murmur with maximum intensity in the third or fourth left interspace near the sternum The murmur is very loud at this site in the center of the precordium and becomes progressively fainter as the examiner moves the stethoscope toward the apex or toward the left clavicle Rarely the murmur is loudest at the left of the xiphoid process Often it is transmitted to the back where it is heard in the left interscapular or subscapular region The murmur of an uncomplicated ventricular septal defect is said to be not usually transmitted to the cervical vessels, in contrast with the murmur of the tetralogy of Fallot But there are occasional exceptions The murmur may endure through part of diastole and obscure the second sound A *thrill* accompanies the murmur in about 90 per cent of the cases [4,5]

In cases with large ventricular septal lesions the nature of the systolic murmur is more variable A thrill may be absent An apical diastolic murmur may be heard in cases with severe defects and very large pulmonary blood flows probably due to functional tricuspid stenosis A pulmonic diastolic murmur may be present as a result of pulmonary hypertension and functional pulmonic insufficiency

The second pulmonic sound may be accentuated and split in the cases with large septal defects

Course and Complications

Frequently in asymptomatic subjects a normal life is terminated by some intercurrent disease Right-sided heart failure with terminal cyanosis is not uncommon in subjects with large defects In Abbott's[1] autopsied series of cases, 37 per cent died of a complicating bacterial endocarditis The vegetations are usually situated in the pulmonary conus of the right ventricle where the shunted stream of blood strikes most forcibly Brain abscess occurs occasionally, more often with uncomplicated ventricular septal defect or tetralogy of Fallot than with any other congenital cardiac anomaly [4,9]

Of interest is the uncommon association of *congenital heart block* [4,8] probably due to a developmental defect of the bundle of His In most cases of congenital heart block there is found a defect of the membranous portion of the interventricular septum [31] Of 14 cases with this conduction disturbance collected by Yater Lyon and McNabb,[423] 26 had a ventricular septal defect and one had no ventricular septum The association of congenital heart block with a ventricular septal defect is attributed to the proximity of the bundle of His to the usual site of the defect near the undefended space, so that the same developmental disturbance is likely to cause both lesions In a recent report of [illegible] cases of congenital heart block, the ventricular septal defect was part of the tetralogy of Fallot in 3, and of Eisenmenger's complex in one [97] Occasionally an atrial septal defect is also present Congenital heart block in itself is not a serious lesion and does not interfere with life The serious prognosis in some cases is determined by associated cardiac anomalies Rarely, Adams Stokes syndrome occurs [98] In the series of 44 cases collected by Yater et al ,[423] symptoms were uncommon and cyanosis was absent in 24 and slight or occasional in 14

Roentgenology

In the cases of small, low interventricular septal defects there is no distinctive cardiac silhouette, but there may be slight enlargement of the right ventricle Occasionally, moderate increases in pulmonary blood flow may be indicated by engorgement of the pulmonary vessels

With large and high interventricular septal defects there are some features similar to those of atrial septal defect with left-to-right shunt, but more striking are features resembling those of patent ductus arteriosus or aortic pulmonic septal defect For as in these conditions blood is transferred from the higher pressure area of the left ventricle to the right ventricle and pulmonary artery Because of the high position and large size of the defect blood passes through the septal defect and pulmonary conus into the pulmonary artery Hence the left ventricular load is increased and the left ventricle becomes enlarged, the pulmonary artery prominent and its smaller branches engorged The aortic knob is small

When pulmonary hypertension is marked or there is an associated overriding of the aorta, there is a right-to left shunt through the

ventricular septal defect, and the roentgenologic findings are those of the Eisenmenger complex (p 749)

Angiocardiography

Even with small shunts the septal defect may be demonstrable by selective angiocardiography (p 15) or rapid biplane angiocardiography With larger high ventricular septal defects conventional angiocardiography discloses continuous reopacification of the right ventricle and pulmonary artery Or the pulmonary artery alone may show reopacification if the contrast material is shunted from the left ventricle through the high defect more directly toward the pulmonary artery than toward the right ventricle proper

Electrocardiogram

There is no significant change in cases with small defects With larger defects incomplete right bundle branch block occurs commonly In cases with high pulmonary arterial pressure the electrocardiogram usually shows evidence of both left and right ventricular hypertrophy [77] Even in the presence of right bundle branch block a deep S wave in V_1 suggests the presence of left ventricular hypertrophy

Cardiac catheterization discloses a significantly higher oxygen content of the right ventricular blood than of the blood in the right atrium owing to the shunt of arterial blood from the left to the right ventricle There is usually an elevation of the pulmonary artery and right ventricular pressures

Surgical Treatment

Methods Ventricular septal defects have been repaired by so-called closed methods or under direct vision [39] In the former a purse string suture is placed in the anterior wall of the right ventricle and through an incision in its center the index finger of the left hand explores the right ventricular chamber for other defects With a large needle a non absorbable suture is passed into the region of the pulmonary conus and directed by the index finger in the ventricular cavity to approximate the anterior and posterior lips of the septal defect The needle and suture are then brought out through the ventricular wall After the septal defect is sutured the myotomy incision is closed by interrupted sutures

Lillehei and associates [56] have employed donors to create a cross circulation (p 1111) and have repaired ventricular septal defects successfully under direct vision with survival of 18 of 25 operated patients Swan and associates [289] refrigerated patients to about 28° and repaired ventricular septal defects under direct vision Du Shane et al [133] repaired ventricular septal defects in 20 children under direct vision with the aid of a mechanical pump oxygenator (p 1114) Sixteen of the 20 survived The period of open cardiotomy varied from 10 to 45 minutes Repair of the ventricular septal defect was accomplished by direct suture in 3 patients and by insertion and suture of a non absorbable polyvinyl (Ivalon) sponge into the opening in the other 17 patients The 16 patients who survived showed pronounced improvement in appetite weight gain increased exercise tolerance and a reduction in pulmonary arterial pressure postoperatively Atrioventricular and intraventricular conduction disturbances occurred in 9 patients

Indications for Surgical Repair There is no indication to repair small ventricular septal defects in patients in whom the left to-right shunt is small and there is no significant pulmonary hypertension At the other extreme also there is no surgical indication in patients with very large defects in whom pulmonary hypertension is so great that the right ventricular pressure is only slightly less than equal to or occasionally exceeds the pressure in the left ventricle and the magnitude of the shunt is very small Operation is indicated in patients with large ventricular septal defects in whom there is a large left to right shunt and pulmonary hypertension is of mild to moderate degree In such cases there will usually be disturbing clinical symptoms and electrocardiographic evidence of right and left ventricular hypertrophy

VENTRICULAR SEPTAL DEFECT WITH AORTIC INSUFFICIENCY

Occasionally a high ventricular septal defect situated just below the aortic valve is associated with a fibrous band which distorts the valve by drawing down one of the cusps and thus renders the valve incompetent [340] Or aortic insufficiency may be due to incomplete support of the medial cusp The physical signs are those of the ventricular septal defect (thrill and loud holosystolic murmur in the second third and fourth left interspace) plus a high pitched diastolic murmur of aortic insufficiency There is a low diastolic pressure due to the aortic insufficiency The electro-

cardiogram shows evidence of left ventricular hypertrophy and sometimes a prolonged P R interval Right ventricular hypertrophy and right bundle branch block patterns have been described in some cases [4, 1] Roentgenologic examination reveals enlargement of the left ventricle and perhaps also of the right and *prominent pulsations of the aorta and pulmonary* arteries Cardiac catheterization may disclose increased oxygenation of blood in the pulmonary arteries Because of the presence of a relatively high oxygen saturation in pulmonary artery blood together with the systolic and diastolic murmurs and evidence of left ventricular hypertrophy, the diagnosis of patent ductus may be made erroneously The clinical course is that of aortic insufficiency with eventual heart failure Bacterial endocarditis may also occur

COR TRILOCULARE BIATRIUM

There is complete or virtually complete absence of the interventricular septum [130] An atrial septum is present but may have a patent foramen ovale or other defect [3, 6] Other congenital cardiac lesions are often present [101, 246] The clinical picture and course *when uncomplicated* are those of a large ventricular septal defect but at least mild cyanosis is usually present

COR BILOCULARE

This occurs rarely About half of the patients with cor biloculare are Mongolian idiots Both the atrial and ventricular septa fail to develop or are vestigial and there is a single atrium a single ventricle and a common atrioventricular canal and valve There may be associated anomalies of the great vessels such as pulmonary atresia [80] common truncus arteriosus anomalous pulmonary veins and persistent left superior vena cava It is amazing that sometimes cyanosis fails to develop in patients with normal arterial trunks, presumably because of a functional if not an anatomic segregation of arterial and venous blood within a single atrium and ventricle As a rule cyanosis is present dyspnea develops and there is evidence of right ventricular hypertrophy

EISENMENGER S COMPLEX[141, 35, 180, 64, 148]

In its narrowest sense this refers to the combination of a ventricular septal defect overriding aorta, right ventricular hypertrophy and a normal or dilated pulmonary artery In the latter item it differs from the tetralogy of Fallot in which the pulmonary artery, valve or infundibulum is stenotic There is now a tendency to include in the Eisenmenger complex also cases of *ventricular septal defect* with a normal aortic root, but with a right to left shunt through the septal defect due to an associated pulmonary hypertension The latter is caused by an increased pulmonary arteriolar resistance of uncertain origin Thus the Eisenmenger complex represents essentially cases with ventricular septal defect and a right to-left shunt either because of pulmonary and right ventricular hypertension (right ventricular pressure equal to left ventricular) or because of an overriding aorta with unoxygenated right ventricular blood entering the aorta and thus reaching the systemic circulation In these cases also pulmonary hypertension is at least a contributory factor It should be noted that cases of the Eisenmenger complex resemble in their pathological physiology (a) cases of patent ductus arteriosus with right to left (reversed) shunt due to pulmonic hypertension and (b) cases of aortic pulmonic septal defect with pulmonary hypertension Furthermore, they resemble also cases of interatrial septal defect with pulmonary hypertension and right to left shunt but in these cases unlike the above there is no increase in left ventricular work and no left ventricular hypertrophy Cases of interatrial septal defect in which a right to left shunt occurs because of associated pulmonic stenosis (with high right ventricular but low pulmonary arterial pressure) are not included in the category of the Eisenmenger complex

There is clinical evidence and evidence from cardiac catheterization that the pulmonary hypertension in Eisenmenger's complex occurs progressively after birth, and that it becomes high enough to cause a reversal in a previous left-to right shunt some time between the ages of 6 and 12 or occasionally later Eisenmenger s complex occurs in those large and high ventricular septal defects in which there is an early large left to-right shunt with augmented pulmonary blood flow and enlargement of the left and right ventricles and pulmonary artery even before the shunt is reversed by severe pulmonary hypertension

The reversal of shunt may occur in infancy or early childhood if there is dextraposition of the aorta

The *clinical picture* is characterized by the relatively late appearance of cyanosis in childhood adolescence or early adult life The cyanosis is usually not as intense as in the tetralogy of Fallot and may occur only on exertion Otherwise the clinical picture is that described under high septal defect

Roentgenologic examination shows enlargement of the right and left ventricles prominent main pulmonary artery with increased vascularity of the mid and peripheral lung fields although the engorgement is often less than that in similar cases with left to right shunts[4]

Angiocardiography shows early opacification of the left ventricle and/or of the ascending aorta simultaneously with the pulmonary artery The increased vascularity of the lung fields distinguishes the Eisenmenger complex from the tetralogy of Fallot The enlarged pulmonary artery of Eisenmenger's complex may not be distinctive because there may be a post stenotic dilatation in Fallot s tetralogy

The *electrocardiogram* shows left or right axis deviation and may disclose evidence of right and left ventricular hypertrophy

Eisenmenger's complex is not amenable to surgical therapy

ISOLATED PULMONIC STENOSIS

Definition

Pulmonic stenosis denotes an impediment to the flow of blood from the right ventricle to the pulmonary vessels at the level of the infundibulum the valve or the main pulmonary artery

Pulmonic stenosis, as part of the tetralogy of Fallot, was always regarded as a common congenital cardiovascular lesion but isolated pulmonic stenosis was formerly considered to be a rare anomaly Largely as a result of cardiac catheterization studies, isolated pulmonic stenosis has now come to be recognized as one of the more common congenital cardiac abnormalities[184, 144, 129, 4, 4, 74, 73, 365] It represents 10 to 12 per cent of cases of congenital heart disease Many relatively large series of cases have been studied and reported[8, 270, 57, [illegible], 358, [illegible], 365]

Isolated pulmonic stenosis also termed pure or solitary' pulmonic stenosis denotes that *the ventricular septum is intact* but according to usage has included the cases with atrial septal defect or patent foramen ovale as well as those with intact atrial septum Pulmonic stenosis with interatrial septal defect (and right ventricular hypertrophy) is sometimes termed the trilogy of Fallot.[2, 8] After the tetralogy of Fallot isolated pulmonic stenosis with interatrial septal communication is the commonest cause of cyanotic congenital heart disease

Age and Sex

Most of the patients are between the ages of 20 and 30 and some between 30 and 50 when the lesion is recognized In the latter group the patients are more likely to be acyanotic Acyanotic patients with isolated pulmonic stenosis below the age of five are rarely seen probably because such patients are asymptomatic and there is no cyanosis to stimulate cardiac investigation There is no significant difference in sex incidence

Pathology

As a rule isolated pulmonic stenosis is the result of stenosis of the pulmonary valve, characterized by a dome like or conical fusion of the pulmonary cusps with a central perforation often only 2 to 4 mm in diameter Or pulmonary stenosis may be caused by scarring and narrowing of the pulmonary annulus and leaflets A bicuspid pulmonic valve is a common finding in valvular stenosis Isolated pulmonic stenosis with intact ventricular septum may also be due to infundibular stenosis[8, 57] In a series of 25 cases of isolated pulmonic stenosis operated by Glover et al [179] there were six instances of infundibular stenosis or of combined valvular and infundibular stenosis, the remaining were purely valvular Stenosis of the main pulmonary artery trunk has been reported and occasionally the narrowing may extend to the left main branch, less often to the right but not beyond

The infundibular stenosis may be located high low or intermediate in the outflow tract and occasionally there is more than one stenosis There is a *membranous type* characterized by a short localized fibrous diaphragm just below the pulmonic valve or more commonly a *fibromuscular type* characterized by a long narrow channel (myocardial infundibular stenosis) In the latter variety the outflow tract is hypertrophied in the membranous type there is a thin walled infundibular chamber In cases of combined infundibular and valvular stenosis the pul

monary artery is frequently hypoplastic The pulmonic valve is frequently bicuspid

The pulmonary artery is usually thin walled and dilated beyond the stenosis (poststenotic dilatation) and the right ventricle is hypertrophied The pathogenesis of the poststenotic dilatation is uncertain It may be due to atrophy of the wall because of the low pulmonary artery pressure, with secondary distention of the atrophic wall Or the distention may be caused by eddies of alternating high and low pressure distal to the stenosis, consequent to the ejection of blood through a constriction at high velocity [12] On the other hand, angiocardiographic and catheterization studies have disclosed that the diameter of the pulmonary artery in pulmonic stenosis varied widely, and that its width could not be correlated with the severity of the pulmonic stenosis as indicated by the pressure in the right ventricle or by the right ventricular pulmonary artery gradient [404] These findings suggested that the dilatation of the pulmonary artery in pulmonic stenosis was a coincident not a related lesion and that the combination represented two different congenital lesions, namely congenital pulmonic stenosis and congenital idiopathic dilatation of the pulmonary artery

The right ventricle is hypertrophied and its wall may be as thick as or thicker than that of the left ventricle The right atrium is usually dilated In fatal cases the organs frequently show signs of passive congestion, cardiac cirrhosis of the liver is especially common

The opening in the atrial septum, when present, was a patent foramen ovale in all the cases reported by Selzer and Carnes,[358] but Campbell[74] observed that true interatrial septal defects occurred with equal frequency There may also be anomalous pulmonary veins draining into the right atrium, in addition to the atrial septal defect Patent ductus arteriosus may be associated with isolated pulmonic stenosis or with pulmonic stenosis and an interventricular septal defect [269, 50a]

The cases of isolated pulmonic stenosis with and without atrial septal communication are presented as a unit because they have essentially similar clinical features, except for the presence of cyanosis in most cases with a septal communication However, this is inadequate to permit an absolute differentiation because cyanosis may be absent despite the communication in cases in which the interatrial shunt is from left to right [269]

Pathologic Physiology[144, 270]

The essential disturbance is an increased pressure in the right ventricle with a normal or diminished pressure in the pulmonary artery (see Catheterization, p 752) The right ventricular hypertension leads to right ventricular hypertrophy Normal cardiac output is maintained despite the obstruction Eventually the right side of the heart may fail, in consequence the cardiac output falls and the right ventricular diastolic, right atrial and systemic venous pressures rise The blood follows its normal pathway when the atrial septum is intact

In cases with patency of the foramen ovale or atrial septal defect there may be no significant shunt or the shunt may be from left to right if there is no rise in right atrial pressure Pressure changes during the cardiac cycle may be such as to produce minor varying left-to-right and right-to-left intermittent shunts In other cases distinct shunts from right to left occur during exercise only and in still others there is a continuous significant right-to-left shunt

In cases of pulmonic stenosis with associated extracardiac aortic pulmonary shunts such as patent ductus with or without ventricular septal defect, the blood flow in the extracardiac shunt is from left to right despite an elevated right ventricular pressure [50a]

Clinical Features

Symptoms and Course In the cases without atrial septal defect, the disease is usually asymptomatic for a long time [3] Sooner or later dyspnea on exertion or fatigability may occur and these are the commonest symptoms Sudden decompensation with right sided heart failure develops commonly in such cases Occasionally there is chest pain or syncope on effort, presumably due to inability of the right ventricle to increase its output during exertion [383, 212] In cases with atrial septal defect cyanosis occurs frequently especially with exertion Continuous cyanosis may appear shortly after birth but most often it appears later, occasionally after puberty or in adult life Cyanosis which appears only on exertion may later become persistent Clubbing of fingers and toes and polycythemia may accompany the cyanosis Squatting occurs occasionally in the cyanotic patients but not nearly as often as in cases of tetralogy of Fal

lot Inadequate weight gain is a common finding in the cyanotic children Pulmonary infections including tuberculosis occur more commonly in association with this lesion than with other congenital cardiac lesions but these have become less important since improvement in public health measures and the advent of antibiotics Right-sided heart failure usually appears in the third or fourth decade and is the chief cause of death The average age at death was 26 years in the series reported by Greene et al [183] but about 10 per cent survive the age of 50 and some live beyond 70 [177] Bacterial endocarditis occurs occasionally Cerebral abscess may be a cause of death in cases in which there is an associated atrial communication

Physical Signs There is a long rough *systolic murmur*, usually maximal in the second left interspace transmitted toward the left cervical region and occasionally to the back Occasionally it is loudest in the third left interspace Stenosis of the infundibulum is more likely to be represented by a systolic murmur in the fourth or third left interspace valvular stenosis by a murmur in the second or third Almost always there is a palpable thrill in the area of maximal intensity of the murmur The second sound may be normal but it is often weak or absent It is usually single sometimes split Occasionally there is a diastolic murmur of pulmonary insufficiency

Roentgenology[207, 139, 49]

In mild cases or early stages of the disease the heart is of normal size in more severe or advanced cases there may be evidence of right ventricular enlargement and the right atrium may also be enlarged if there is a significant atrial septal defect In these cases also the pulmonary vascular markings are diminished and the pulmonary fields may appear unusually clear However in the occasional cases of pulmonic stenosis and interventricular septal defect in which the shunt is from left to right the pulmonary fields may show normal or increased vascularization [10, 141] This applies also to occasional cases of pulmonary stenosis with interatrial septal defect in which a left to-right shunt is associated with an increased pulmonary blood flow [141]

In cases with valvular stenosis the usually associated post stenotic dilatation of the pulmonary artery produces a *marked convexity of the middle left cardiac salient* just below the aortic knob Its pulsations are prominent Rarely this is of aneurysmal size The main branches of the pulmonary artery are usually of normal or diminished size and their pulsations diminished The association of a prominent main pulmonary artery of increased pulsation, with diminished pulsation of the left and right pulmonary arteries and clear lung fields is diagnostic of pulmonic stenosis In occasional cases of valvular stenosis without post stenotic dilatation the pulmonary artery salient is normal In the rare instance of isolated pulmonary infundibular stenosis the pulmonary artery segment is usually small Post stenotic dilatation may involve the distal portion of the infundibulum and the pulmonary conus may form a prominent convexity on the left border above the left ventricular contour

When pulmonic stenosis is associated with post stenotic dilatation and a prominent pulmonary artery shadow, its roentgenologic appearance simulates the various conditions associated with pulmonary hypertension and a large pulmonary artery namely atrial or ventricular septal defect or patent ductus Fluoroscopic study of the pulmonary artery pulsations and of the peripheral pulmonary vascular field aids in diagnosis (p 795)

Angiocardiography

This is not usually of major diagnostic importance except to determine the presence of complicating lesions However the stenosis itself is more commonly demonstrable in cases in which it is isolated than when associated with interventricular septal defects [183] This is seen as an interruption in the flow of contrast medium at the site of the pulmonic valve or a narrowing in the infundibulum The actual site of the stenosis may be demonstrable more regularly by the rapid biplane method of Lind (p 15) or by selective angiocardiography after direct injection of the contrast medium into the outflow tract of the right ventricle (Fig 10 p 16) Angiocardiography confirms the presence of right ventricular enlargement and dilatation of the main pulmonary artery It may also indicate the presence of an interatrial shunt by early opacification of the left atrium from the right

Electrocardiography

This usually shows right axis deviation (occasionally left axis deviation) [5] right ventricular hypertrophy or incomplete right bundle branch block [1, 8] [5] In mild cases there may be no axis deviation In severe cases

with right ventricular hypertrophy there is usually a tall R wave, S-T segment depression and T wave inversion in V_1 and other right precordial leads. The height of the R wave diminishes after successful operation.[185, 44, 46, 24] There may be tall P waves especially in lead II suggesting atrial hypertrophy.

Cardiac Catheterization: Pressures and Oximetry

The striking and *diagnostic finding* is the *elevation of right ventricular pressure with a relatively low pulmonary artery systolic pressure, and with a consequent significantly increased gradient between them.* Normally the gradient is minimal, the pulmonary artery and ventricular systolic pressures being virtually identical. As the catheter is withdrawn from the pulmonary artery to the right ventricle, a ventricular septum because in the presence of a large ventricular septal defect right and left ventricular pressures are equal. Although the pulmonary artery pressures are relatively less, their absolute values are normal or very slightly diminished. In the presence of infundibular stenosis, as the catheter is withdrawn, the systolic pressure in the pulmonary artery and that in the infundibulum distal to the stenosis are the same (Fig. 130). Proximal to the stenosis there is a rise in systolic pressure in the infundibulum and this remains the same in the rest of the right ventricle. The diastolic pressure falls as the catheter is withdrawn from the pulmonary artery past the pulmonic valve and remains constant in the right ventricle both proximal and distal to the infundibular stenosis.

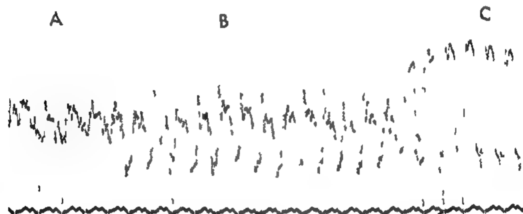


Fig. 130. Pressure readings in a case of pulmonary valvular stenosis as intracardiac catheter is withdrawn from pulmonary artery (A) to infundibulum (B) to right ventricle (C). Pulmonary pressure 37/13, infundibular pressure 38/7, right ventricular pressure 61/6 mm. Hg.

characteristic pressure curve, showing a sharp rise, is produced. In mild or moderate cases the right ventricular systolic pressure ranges from 40 to 100 mm. Hg, and in very severe cases it is usually above 100 mm. Hg. However, there is no close correlation between clinical severity and right ventricular pressures in individual cases; asymptomatic patients may have right ventricular systolic pressures exceeding 100 mm. Hg. In the relatively milder cases reported by Joos et al.[274] it ranges from 28 to 134 mm. Hg; in the severe cases reported by Blount et al.[46] from 110 to 221, with an average of 168 mm. Hg. In the acyanotic cases the right ventricular systolic pressure occasionally exceeds that in the systemic arteries. This denotes closure of the

In combined valvular and infundibular stenosis, there is a rise in systolic pressure when the catheter is withdrawn from the pulmonary artery into the infundibulum (between the valvular and infundibular stenoses) and a further rise as the catheter is drawn proximal to the infundibular stenosis. The right atrial pressure is usually normal unless there is right sided heart failure. In cases with atrial septal defect the right atrial pressure may be slightly elevated. Occasionally the catheter passes through the atrial septal communication, then it may be determined that left and right atrial pressures are approximately equal, or one or the other is slightly higher.

Oxygen saturation is normal in the various

chambers if the atrial septum is intact When there is an atrial septal communication the oxygen content of right atrial blood is significantly higher than that in the vena cava Identical oxygen concentrations in the right atrial and right ventricular blood exclude a ventricular septal defect

Surgical Treatment

Surgical treatment is generally effective and consists of direct enlargement of the stenotic passage sufficiently to diminish greatly or abolish the ventricular infundibular or ventricular pulmonic gradient [254, 55, 55b, 318, 4, 75, 365]

Exact *indications* have not become stabilized but are being extended as the technical procedures and results improve and as surgical mortality diminishes Operation is indicated in isolated pulmonic stenosis in which cyanosis is caused by a right to left interatrial shunt It is indicated in patients with or without cyanosis if the pulmonic stenosis produces considerable disability due to exertional dyspnea or fatigability Finally it may be indicated whether or not cyanosis or symptoms are present if severe hemodynamic disturbances are present as denoted by a right ventricular systolic pressure of more than 75 to 100 mm Hg or a gradient of more than 45 to 70 mm Hg or if there is electrocardiographic evidence of marked right ventricular hypertrophy On the other hand there is no indication for operation at present on acyanotic asymptomatic patients with right ventricular pressures of less than 75 mm Hg Silverman et al [365] observed a good correlation between the electrocardiographic findings and right ventricular systolic pressures below and above 100 mm Hg All 20 of their 50 patients with pressures of 100 mm Hg or more showed one or several of the following (1) an R wave in V_{4R} or V_1 of 20 mm or over (2) P pulmonale" i e peaked P waves of 3 0 mm or more in lead II and right precordial leads (3) S T segment depressions and T wave inversions in right precordial leads Those with right ventricular pressures below 100 mm Hg sometimes had tall R waves in right precordial leads but less than 20 mm there were no S T and T wave alterations or P pulmonale

The preferred age for operation appears to be between 5 and 20 since operative mortality has been higher in cases outside this age range But sometimes it is necessary to operate during infancy when severe pulmonary stenosis is associated with right sided congestive heart failure Medical measures to control the heart failure should be administered preoperatively but only for a brief period

Surgical Procedure Until recently the preferred operative procedure was the Brock type of transventricular valvulotomy The Brock procedure refers to resection and dilatation of the pulmonary valve[55] or resection of an infundibular stenosis[55b] through an incision in the right ventricle without direct palpation or visualization of the stenosis More recently, open' procedures permitting correction of the lesion under direct vision have been used with the aid of hypothermia or of a donor cross circulation with venous inflow occlusion or by a pump to by pass the right heart The Blalock subclavian pulmonic or the Potts aortic pulmonic shunt type of operation employed in cases of the tetralogy of Fallot is contraindicated in isolated pulmonic stenosis Cyanotic patients with pulmonic stenosis and atrial septal defect in whom a Blalock operation was performed because of a mistaken diagnosis of tetralogy of Fallot eventually suffered severe heart failure with pulmonary congestion This was due to the fact that the left atrium postoperatively received not only right atrial blood through the septal defect but also a greatly increased pulmonary venous return due to the improved pulmonary circulation

Access to the heart is obtained by a parabolic inframammary incision through the third left anterior intercostal space The presence and site of valvular or infundibular stenosis are readily ascertained In valvular stenosis the post-stenotic dilatation of the main pulmonary artery is observed and a systolic thrill is palpable just distal to the valve The thrill may be abolished by digital invagination of the pulmonary artery with obliteration of the valve In infundibular stenosis the thrill is felt over the wall of the outflow tract distal to the infundibular stenosis and proximal to the valve A thin walled infundibular chamber but no post stenotic dilatation of the pulmonary artery, is seen in isolated infundibular stenosis

Valvular stenosis is corrected by making a small incision through the right ventricular wall inserting a probe to explore the stenotic area and following with a valvulotome designed with a spearhead blade with a short

blunt tip With the latter instrument the valve is repeatedly resected with progressively wider blades and further dilated by a series of sounds A similar procedure has been performed by retrograde approach to the valve through an incision in the pulmonary artery[389]

Infundibular stenosis is corrected by first passing a resecting rongeur through a right ventricular incision and exploring the ventricle with it to ascertain the site and nature of the stenosis Then the jaws of the resector are opened to engage the full crest of protruding tissue and the tissue cut away repeatedly For adolescents and older patients a more thorough resection has been claimed by use of a guillotine type of knife such as is used in mitral valve surgery, and by use of a large dilator for the valvular stenosis, such as is used in the surgical treatment of aortic stenosis

A successful surgical procedure should be checked at the time of operation by demonstrating that the ventricular pulmonary or ventricular infundibular gradient has been minimized (to less than 10 mm Hg) or abolished There should also be apparent an increased pressure of the infundibulum and pulmonary artery and generalization of the previously localized thrill

Open valvuloplasty has been used to correct pulmonic stenosis, because of dissatisfaction with the blind approach of the Brock procedure Dodrill and associates[1,3] reported the performance of pulmonary valvuloplasty under direct vision using a mechanical heart for a complete by pass of the right side of the heart, in a case of pulmonic stenosis Swan and associates[389] have corrected pulmonic stenosis by a transarterial (pulmonary artery) approach after hypothermia has been induced (p 1112) to permit cessation of the circulation and direct visualization of the lesion

The chest is entered by a transverse sternum splitting incision through the fourth intercostal space on the right and the third intercostal space on the left The azygos vein is ligated and ligatures placed around the venae cavae The pulmonary artery is clamped distally to avoid back bleeding A Potts curve-toothed aortic clamp is placed longitudinally on a bite of the main pulmonary artery just distal to the valve ring a small incision is made into this bite of aorta and the ligatures on the venae cavae are promptly tened to cut off the blood flow into the heart The heart beats at a slow rate of 4 to 10 per minute and after a few beats the right ventricle is emptied of blood and the operative field is dry The conical stenotic valve is clearly visualized its tip grasped with a toothed forceps and an incision made with a scissors from the lumen of the valve to the valve ring A second incision is made 180 degrees away again extending from the valve opening clear to the base of the valve The valve is thus divided into two cusps with commissures If the valve rim is too thick or the cone very long the distal segment of the valve is excised The finger or an instrument is inserted through the valve into the right ventricle to exclude the presence of an associated infundibular stenosis The entire chest and especially the entire heart is flooded with Ringer s solution to expel air through the open pulmonary artery and thus to avoid air embolism The ligature on the superior vena cava is released to allow blood to mix with the Ringer s solution then the clamps on the aorta and pulmonary artery are removed and finally the ligature on the inferior vena cava Blood flow is now restored The incision in the pulmonary artery is sutured hemostasis effected the thorax closed and postoperative pleural drainage set up The patient is then rewarmed (p 1113) The entire operative procedure can usually be performed during three or four minutes of total occlusion and an additional minute for occlusion of the inferior vena cava

Operative Mortality and Results The mortality rate is equally low in the closed and open procedures for *valvular stenosis*, generally below 10 per cent but more recently well below 5 per cent[56, 173, 41, 388, 216, 21a] However resection of an infundibular stenosis by the Brock technique is associated with a mortality rate of about 15 per cent

Clinical improvement in terms of disappearance of cyanosis, amelioration of other symptoms and increased exercise tolerance has likewise been excellent in the great majority of cases, regardless of technical approach On the other hand comparative preoperative and postoperative hemodynamic studies have disclosed inconstant and frequently inadequate reductions in right ventricular pressure and insufficient diminution of the ventricular pulmonary gradient[268, 281, 46, 34, 216] (Fig 131) Swan et al[388] have reported that transpulmonary valvuloplasty under direct vision had afforded more uniformly satisfactory results with complete reduction of right ventricular pressure virtually to normal and complete or almost complete elimination of the gradient across the obstruction Thus in operations by the closed technique Blount et al[46] reported that the right ventricular systolic pressure *fell from* an average of 168 mm Hg preoperatively to an average of 65 mm Hg postoperatively *still* leaving a persistent postoperative gradient which averaged 43 mm In the group operated on transarterially under direct vision, the

average preoperative right ventricular systolic pressure was 116 mm Hg and fell postoperatively to normal in every case The average postoperative systolic pressure was 28 mm Hg Since the average postoperative pulmonary arterial pressure was [illegible] mm Hg the average gradient was only about 6 mm Hg after operation

Diminution in the intensity of the systolic murmur increased intensity of the second pulmonic sound occasional appearance of a pulmonic diastolic murmur presumed to be due to induced pulmonary insufficiency of no clinical significance, slight postoperative increase in transverse diameter of the heart and diminution in electrocardiographic signs of

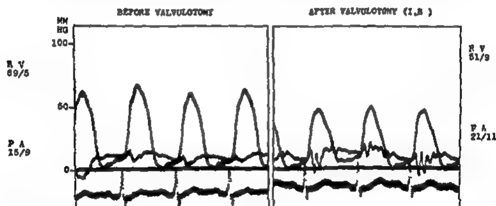


Fig 131 Simultaneous pressure pulses in a case of pulmonary valvular stenosis before and after valvulotomy Note systolic right ventricular pulmonary artery gradient of 54 mm Hg moderately reduced to 30 mm Hg following Brock type of valvulotomy (Courtesy Dr A Gordon)

right ventricular hypertrophy are among some of the results of the operation Transient heart failure and subacute bacterial endocarditis have been observed postoperatively

THE TETRALOGY OF FALLOT

The combination of a ventricular septal defect with pulmonic stenosis dextroposition of the aorta and right ventricular hypertrophy is known as the tetralogy of Fallot [153] It is the commonest clinical form of congenital heart disease in adult life which is associated with cyanosis and clubbed fingers Tetralogy of Fallot does not refer to a sharply defined pathologic entity since the location and character of the pulmonic stenosis the nature and size of the ventricular septal defect and the degree of dextroposition vary greatly, individually and in combination

Embryology and Pathogenesis

Cephalad to the primitive ventricle and separated by a fold is another chamber termed the bulbus arteriosus, this in turn is similarly demarcated cephalad from the truncus arteriosus During the fifth to the eighth weeks the proximal (caudal) portion of the bulbus is absorbed into the right ventricle as the infundibulum or the pulmonary conus arteriosus The remainder of the bulbus and the truncus arteriosus are divided by a spirally (clockwise) twisted septum to form the pulmonary artery and the aorta As noted above (p 744) this septum also grows caudally to help form the membranous part of the interventricular septum and thereby to close the interventricular foramen The normal growth and twist of the truncus bulbar septum is such as to cause the pulmonary artery to arise from the right ventricle and the aorta from the left ventricle

The pathogenesis of the lesions forming the tetralogy of Fallot and similar combinations of malposition of the great vessels has been the subject of controversial theories which have been reviewed by Lev and Saphir [249] These authors applied the studies of Pernkopf and Wirtinger[318] to their own cases and reached the conclusion that the basic abnormality is a disturbance in the absorption of the bulbus as first postulated by Keith [232] This disturbance is said to be due to an excessive backward torsion of the proximal portion of the bulbus

An ingenious theory supported by many

case studies was formulated by Spitzer[375] who attributed the lesions in the tetralogy of Fallot to two essential factors (1) An inadequate clockwise torsion or even a counter clockwise torsion of the truncus and bulbus arteriosus (see above) and of the septum which divides this vascular tube (2) Persistence of the reptilian right aorta which should atrophy if development is normal

A new ontogenetic theory has recently been proposed by de la Cruz and da Rocha[115]

Pathology[16]

Since the proper development of the truncus and bulbus arteriosus and their common septum determines the normal position and size of the aorta and pulmonary artery and the completion of the interventricular septum it is obvious that a disturbance in that development would cause not a single but multiple defects Hence the frequency of the tetralogy of Fallot as compared with uncomplicated malposition of the great vessels Most often the aorta appears displaced to the right so as to arise from both ventricles (reitende or riding aorta), or it may arise from the right ventricle alone (simple transposition or dextroposition of the aorta) Occasionally the origin of both vessels is transposed the aorta arising from the right and the pulmonary artery from the left ventricle (crossed or complete transposition of the great vessels) (p 762) The positions of the aorta and pulmonary artery may appear reversed with respect to each other, but their origin is from the proper ventricle (corrected transposition)[37] The degree of dextroposition of the aorta in the tetralogy of Fallot is very variable The operative results have been poor when most of the aorta arises to the right of the ventricular septum

The pathology of pulmonary valvular, pulmonary infundibular and pulmonary arterial stenosis has been described (p 749) In an anatomic study of 48 hearts with the tetralogy of Fallot,[68] there was infundibular stenosis alone in 16 combined infundibular and valvular stenosis in an additional 27 In 2 there was only valvular stenosis and in 3 only pulmonary atresia Surgical experience indicates a considerably higher incidence of solitary or predominant valvular stenosis in cases of tetralogy of Fallot

If the pulmonic stenosis is severe or the pulmonary artery or valve is completely occluded (pulmonary atresia), the ductus arteriosus must be patent to permit life The ductus may communicate with the pulmonary artery, which is patent distal to the atretic portion Death usually supervenes after a few months as the ductus becomes obliterated Rarely a blood supply to the lungs is maintained by the development of a remarkable collateral circulation arising from the aorta or its branches[6] as in cases of persistent truncus arteriosus with bronchial arteries supplying the lungs The collaterals consist of dilated bronchial, esophageal, thyroid mediastinal or other vessels

The ventricular septal defect, the third element in the tetralogy of Fallot, is usually at the upper portion of the interventricular septum, anterior to the undefended space Occasionally the entire septum is lacking

The right ventricle is considerably hypertrophied In most cases its wall is thicker than that of the left ventricle When the site of the pulmonary stenosis is in the infundibulum a third (accessory) ventricular chamber may be formed in the right ventricle just above the stenosis

In about three quarters of the cases of tetralogy, the aortic arch is on the left, in one quarter on the right In 12 to 20 per cent of the cases there is an associated aberrant right subclavian artery[318]

A tendency to the development of widespread pulmonary thrombosis has been reported by Rich[3]

The so called *pentalogy of Fallot* refers to the four elements of the tetralogy in combination with patency of the foramen ovale or interatrial septal defect[149] In a series of 25 necropsy cases of tetralogy of Fallot, 10 were found to have a functional atrial septal defect, averaging 9 by [illegible] mm, but not correlated with any of the clinical features[52]

Pathologic Physiology

As a result of the pulmonic stenosis, the right ventricular pressure and the work of the right ventricle are increased and the chamber becomes enlarged and its wall hypertrophied (See Cardiac catheterization p 759) Right ventricular venous blood is shunted through the interventricular septal defect into the overriding aorta The aorta also receives oxygenated blood from the left ventricle and the total systemic blood flow exceeds that through the narrowed pulmonary artery The subnormal pulmonary blood flow[35] and consequent deficiency in arterial oxygenation are

fundamental elements in the circulatory disturbance (See p 732 for cardiac output and size of shunt) Arterial oxygen unsaturation results in cyanosis and in polycythemia

Clinical Features

The tetralogy of Fallot is the one form of congenital heart disease which accounts for the great majority of cases of persistent cyanosis and clubbing in adolescence and adult life (morbus caeruleus) *Cyanosis* is present from infancy It may be absent or slight in the first few months of life while the ductus arteriosus is still patent and serves as an accessory route for blood (from the aorta) to reach the pulmonary circulation However there are cases of tetralogy of Fallot called acyanotic because of the absence or virtual absence of a right to left shunt at rest There were ten such cases among 80 collected by Wood et al [4,5] Rowe et al [342] reported four cases of atypical tetralogy of Fallot without cyanosis and with increased pulmonary vascularity despite pulmonic stenosis *Clubbed fingers* usually appear months or years after the appearance of cyanosis Eventually clubbing may be marked while the cyanosis is only slight The cyanosis may become intensified during exercise pulmonary infections and late in the course of the disease when right sided heart failure develops The increased cyanosis on exercise may be due to the inability of the increased venous return to pass the pulmonary stenosis hence more of the venous return is shunted from right to left into the aorta *Cyanosis retinae* is usually present and occurs early *Suffusion of the eyeballs* is often associated with secondary *polycythemia*

The pathogenesis of cyanosis and clubbing *in congenital heart disease was discussed* above (p 731 732)

Dyspnea on exertion is a common complaint Paroxysmal attacks of dyspnea may occur generally after exercise, and accompanied by an intensification of cyanosis Exercise may induce syncope Orthopnea is absent in fact the dyspnea may be intensified when the patient is erect (orthostatic dyspnea) Fatigability and weakness are frequent symptoms Characteristically the child with tetralogy of Fallot assumes the squatting or knee-chest position when dyspneic or tired from exertion The physiology of the squatting position is uncertain It is presumed that the peripheral systemic resistance is somehow increased the aortic and left ventricular pressure raised and thereby the right-to left shunt diminished Or else the venous return is diminished and a greater percentage of the unoxygenated blood passes by way of the pulmonary artery Arterial oxygen saturation is promptly increased by squatting

Polycythemia often of intense degree is usually present The blood volume is increased primarily due to an increase in red cell volume [398] The hematocrit is very high Quite frequently and especially in the late stages of the disease patients suffer from dizziness, syncopal attacks epileptiform convulsions and transient or permanent paralyses Death may occur during a syncopal attack These cerebral symptoms are secondary to anoxia of the brain and are probably related to the vascular disturbances associated with polycythemia Cerebral thrombosis, encephalomalacia and cerebral hemorrhage may occur Epistaxis hemoptysis and hematemesis have also been reported as resulting from the polycythemia Brain abscess is more often associated with this than with any other congenital cardiac lesion [3,9] Orthostatic albuminuria due to disturbance of the renal circulation has been noted The patients with tetralogy of Fallot may be of normal intelligence or they may be mentally and physically retarded

Cardiac Signs Usually there is a *systolic murmur* to the left of the sternum in the second or third interspace occasionally in the fourth It has been claimed that the lower location corresponds to an infundibular stenosis the higher to a pulmonary valvular or arterial stenosis The murmur may or may not radiate to the cervical vessels The *systolic murmur is usually absent in pulmonary atresia*

A systolic *thrill* is often present but less frequently than in uncomplicated cases of pulmonic stenosis or ventricular septal defects

The *second pulmonic sound* is weak or absent but occasionally it is normal In pulmonary atresia and occasionally in pulmonary stenosis the second pulmonic sound is normal or loud and clear and presumably represents the second aortic sound transmitted from the dextroposed aorta There is no diastolic murmur The presence of the latter suggests some other lesion or an additional lesion besides the tetralogy of Fallot

Precordial bulging systolic pulsation in the

second and third interspaces and epigastric pulsation may result from the hypertrophy of the right ventricle

Roentgenology

The roentgenologic findings have been described by Pipp[307] The following are the usual features after the first few years of life when the heart appears small or only slightly enlarged



Fig 132 *A* Tetralogy of Fallot Coeur en sabot configuration
B Angiocardiogram of same case Simultaneous opacification of aorta and pulmonary artery



Fig 133 Tetralogy of Fallot *A* Posteroanterior view Note coeur en sabot configuration is not present
B Angiocardiogram of same case Left oblique view Simultaneous opacification of aorta and pulmonary artery

1 The left lower contour is plump and prominent and the apex is elevated and blunted resembling a sheep's nose The blunting of the left contour, often associated with a transverse rectangular enlargement gives rise to the description of *coeur en sabot* (like a wooden shoe) (Fig 132) This contour represents the hypertrophied and rotated right ventricle This differs from the aortic configuration (p 689) in which the left lower contour is elliptical and not cut off, and in which oblique views disclose enlargement of the left ventricle not of the right In general the cardiac enlargement in tetralogy of Fallot is not pronounced, and the coeur en sabot

configuration is usually absent in children (Fig 133)

2 In some cases the waist of the heart forms a concave depression i e, *the left mid dle contour formed by the pulmonary artery* is small or absent In the left anterior oblique view the pulmonary window is abnormally clear There is no pulmonary congestion The hilar pulmonary vessels are usually small and their pulsations are not visible These findings contrast with the prominent pulmonary arterial shadow in Eisenmenger's tetralogy and in atrial septal defect In other cases the left border of the heart is straight or convex and the pulmonary salient may be prominent This depends on the size of the pulmonary artery In valvular stenosis with post stenotic dilatation the latter causes a prominence of the pulmonary salient But in these cases also the pulmonary branches are small and the pulmonary fields are clear owing to dimin ished vascular markings

3 The shadow of the great vessels may be narrow in the anterior posterior view but the aortic shadow becomes wider and prominent in the left-anterior-oblique view

4 In about 20 to 25 per cent of cases there is a right aortic arch (p 781) visible as a prominence of the aortic knob to the right of the sternum within the shadow of the su perior vena cava

Angiocardiography[1, 8, 210]

There is a prompt passage of the Diodrast from the right ventricle simultaneously into the aorta and pulmonary artery The aorta and all its branches are visualized within 3 seconds after injection instead of in 5 or 6 seconds as is normal Relatively little of the contrast media enters the pulmonary artery whereas a normal or large pulmonary artery is visualized in Eisenmenger's tetralogy

The opacification of the aorta is not only prompt but dense in contrast with the early but faint opacification which may occur with atrial septal defects The exact site and na ture of the stenosis are demonstrable in not more than 20 to 50 per cent of cases and somewhat better with rapid biplane angio cardiography[211] Angiocardiography is of value also in disclosing the anatomy of the aortic arch and subclavian arteries in differentiating other cyanotic cardiac anomalies (such as pul monic stenosis with interatrial communica tion Eisenmenger complex and transposition of the great vessels) and in detecting as sociated anomalies such as a *persistent left* superior vena cava which may obscure the operative field It is also of value in disclosing *the availability of a pulmonary artery to be used for the Blalock anastomosis*

The left anterior oblique or left lateral views are ordinarily used in angiocardiography to visualize the two sides of the heart simul taneously but in some cases the opacified superior vena cava or dextroposed aorta ob scures the outflow tract of the right ven tricle in these projections Marder and Scott[212] found that the right anterior oblique projec tion provided unobstructed visualization of the infundibulum of the right ventricle and was valuable in demonstrating the infundibu lar stenosis seen in the tetralogy of Fallot es pecially by the technique of biplane right-angle serial exposures

The Electrocardiogram

There is usually a pronounced right axis deviation and there may be an RS T de pression and an inverted T in leads II and III Electrocardiographic evidence of right ven tricular hypertrophy was found in all of a series of 52 cases studied by Woods[47] es pecially in the precordial leads (p 115) Tall pointed P waves were found in 35 per cent especially in lead II

The Circulation Time

The injection of 3 minims of ether diluted with 10 minims of saline produces pares thesias of the lips and extremities due to the drug's entrance into the systemic circulation[29] Arm to-tongue (saccharin) time may be abbreviated almost to the ether time since the saccharin passes directly into the systemic circulation by way of the shunt without traversing the pulmonary circulation as it usually does The right ventricle-to-ear time may be determined by injecting Evans blue dye (T 1824) into the catheter placed in the right ventricle and determining its time of ar rival in the ear by an ear oximeter Normally the time is 8 to 10 seconds In the tetralogy of Fallot it is less than 5 seconds In other right to-left shunts such as pulmonary stenosis with interatrial septal defect the time is usually be tween 6 and 8 seconds

Cardiac Catheterization

The right ventricular pressure is elevated *The pulmonary arterial pressure is lower than that in the right ventricle* denoting pulmonary stenosis Occasionally the catheter may pass through the ventricular septal defect from the

right ventricle into the aorta The establishment of the type of stenosis by successive pressure measurements as the catheter is withdrawn from the pulmonary artery to the infundibular region to the right ventricle has been described (p 752) The right ventricular aortic and systemic arterial pressures are equal when the septal opening is large and the aorta considerably dextroposed

The *oxygen concentration* in the right ventricle significantly exceeds that in the right atrium as in other cases of ventricular septal defects

In many cases of tetralogy of Fallot the flow in the pulmonary capillaries exceeds that in the pulmonary artery indicating a significant collateral circulation to the lungs,[35] but the effective pulmonary blood is still diminished The pulmonary blood flow in Eisenmenger's complex is normal or increased

Oximetry

The resting arterial oxygen saturation is usually between 70 and 85 per cent with a range between 45 and 90 During exercise, continuous recordings with the Millikan ear oximeter have disclosed a striking fall in oxygen saturation[289] which is associated with an increase in cyanosis In normal persons there is no reduction in oxygen saturation during exercise Furthermore, patients with the tetralogy of Fallot experience a fall in oxygen consumption per liter of *ventilation during exercise* whereas normal individuals consume more oxygen per liter of ventilation under the same conditions Patients with the tetralogy of *Eisenmenger may experience a fall in oxygen* saturation during exercise but their $\frac{\text{oxygen consumption}}{\text{ventilation}}$ ratio rises in normal fashion [illegible] When normal persons breathe 100 per cent oxygen the arterial oxygen saturation rises from about 97 per cent to 100 per cent within three minutes Patients with tetralogy of Fallot require 10 to 15 minutes under the same circumstances to reach maximum oxygen saturation (which is still below normal)[200]

Differential Diagnosis (p 793)

Course and Complications of Tetralogy of Fallot

Most patients with the tetralogy of Fallot die in the first two decades of life as a result of congestive heart failure cerebral lesions complicating polycythemia bacterial endocarditis or pulmonary infections including tuberculosis Occasionally, however, patients reach adult life and are capable of normal activity with few symptoms The greatest longevity was reported in the case of a famous American musician who died of a stroke at the age of 59[418] Middleton and Ritchie[285] reported another case of tetralogy of Fallot in which death from congestive heart failure occurred at 45

Surgical Treatment

Blalock Taussig Operation and Aortic Pulmonary Shunt The objective of these operations for Fallot's tetralogy is to increase the pulmonary blood flow and the oxygenation of *blood by anastomosing a systemic artery to a* pulmonary artery These operations are indicated for other congenital cardiac lesions with diminished pulmonary blood flow, including tricuspid atresia pseudotruncus arteriosus single ventricle with pulmonary stenosis and some cases of pulmonary atresia Shunt operations are feasible only if there is a pulmonary artery or branch of sufficient size to receive the blood flow from a systemic artery For this reason, among others, angiocardiography may be necessary to obtain exact anatomic knowledge of the anomalies especially if a direct attack is considered

In the procedure devised by Blalock and Taussig[43] a subclavian or innominate artery is anastomosed end to-side (occasionally end to end) to the right or left pulmonary artery, near its origin In the procedure of Potts *Smith and Gibson*[319] a direct side-to-side anastomosis is made between the aorta and pulmonary artery, with the aid of a clamp which does not completely interrupt the circulation *in these vessels during* the anastomosis Blalock usually makes his incision in the third right interspace but when preoperative examination reveals a right aortic arch, the incision is on the *left side* Potts performs an aortic pulmonary anastomosis on the left side if there is a normal left aortic arch a subclavian pulmonary anastomosis also on the left side if there is a right aortic arch

Ideally patients should be operated upon between the ages of three and twelve The severity of anoxemia incapacity, dyspnea and degree of reduction in pulmonary blood flow response to exercise and failure to gain weight are factors determining the urgency of the operative procedure

The *results* of successful operation are often dramatic and the clinical improvement

striking[307, 317] The pulmonary blood flow and oxygen saturation are increased Cyanosis disappears and exercise tolerance is greatly improved so that previously incapacitated children can run and play However there is some enlargement of the heart postoperatively It is theoretically probable that many of these operated patients will subsequently succumb to congestive heart failure as do patients with congenital patent ductus arteriosus or other arteriovenous shunts However during the period that has elapsed there have been remarkably few instances of heart failure due to this cause

The mortality rate in the first 857 operations performed by Blalock varied from 11 to 25 per cent according to the age group with an over all mortality of 15 7 per cent and an additional 2 per cent mortality in the 8 months following the operation[307] The clinical result was good in 77 3 per cent and fair in an additional 3 9 per cent only 3 1 per cent being unimproved Operative complications included cardiac arrest hemorrhage cerebral thrombosis hemorrhagic pleural effusions pulmonary edema pneumothorax and local thrombosis at the anastomotic site In some cases the operation could not be completed because the pulmonary pressure was too high there was a single pulmonary artery the pulmonary arteries were too small or the systemic artery was too short to permit anastomosis In 4 per cent there was an incorrect preoperative diagnosis of tetralogy in patients found to be suffering from complete transposition of the aorta a single ventricle with pulmonic stenosis pseudotruncus arteriosus and others Bacterial endocarditis or cerebral abscess occurred occasionally in the first few months or first few years after the operation In a series of 500 operations for cyanotic heart disease Potts[318] reported a mortality of 15 per cent among children from 2 weeks to 3 years of age but only 2 8 to 4 6 per cent in those beyond the age of 3 years

In a report of 200 cases of cyanotic congenital heart disease essentially the tetralogy of Fallot operated on over a 4 year period Campbell and Deuchar[76] noted an operative mortality of 12 per cent and good or very good results in 68 per cent In the 165 cases of tetralogy of Fallot alone the operative mortality was 8 5 per cent and good results were obtained in over 75 per cent They commented that the improvement in comparison with the preoperative state was especially dramatic at first but that in time it appeared less striking because of comparison with the state of the normal child

Valvulotomy and Infundibular Resection for Tetralogy of Fallot The Blalock anastomosis does not alleviate the anatomic abnormalities in the tetralogy of Fallot and produces an additional anomaly a patent ductus Therefore, despite the encouraging and often dramatic results observed with that procedure efforts have been made to attack the tetralogy directly and to repair the anatomic disturbances responsible This has been accomplished primarily by pulmonary valvulotomy when the stenosis was located at the valve or by infundibular resection in cases of infundibular stenosis or by both The procedures have been described (p 753) In 30 cases thus treated there was an over all mortality of 23 3 per cent 20 per cent in cases of valvular and 33 3 per cent in cases of infundibular stenosis This was regarded as not significantly higher than the mortality in the early series of cases operated on by the Blalock procedure Campbell Deuchar and Brock[78] reported the results in 100 patients with Fallot s tetralogy operated on by the direct procedure 45 of them had infundibular resection alone and 55 a pulmonary valvulotomy but 18 of these required an infundibular resection as well The gross mortality was 11 per cent in cases operated on by valvulotomy 18 per cent in those operated on by infundibular resection These compared with an 8 per cent mortality rate found by the same authors in 165 cases of Fallot s tetralogy treated by the Blalock shunting procedure Two thirds of the patients treated by the direct procedures obtained good or very good results the results being better in those who had an infundibular resection and survived than in those subjected to valvulotomy An Eisenmenger syndrome is not produced by the operation possibly because considerable stenosis persists and there is still a large ventricular pulmonary pressure gradient across the site of stenosis It is dubious that these incomplete direct procedures are preferable to the Blalock shunting operation as long as the operative risk is greater in the former

Intracardiac Surgical Correction by Direct Vision Pulmonary valvulotomy and infundibular resection attempt correction of only

one part of Fallot's tetralogy and this is imperfect because the procedure is relatively blind (p 753) Lillehei and associates[55] reported the correction of both the pulmonic stenosis and the interventricular septal defect under direct vision with the aid of cross circulation and by complete by pass of the heart and lungs with the aid of a pump oxygenator[67] Apparently the septal defect can be closed despite some persistent overriding of the aorta In a case of pentology of Fallot the atrial as well as the ventricular septal defect was closed and the pulmonic stenosis relieved by valvulotomy Direct vision intracardiac correction of the defect may also be accomplished by the aid of hypothermia but the use of a pump-oxygenator heart lung by pass is now replacing all other techniques (p 1113)

PULMONARY ATRESIA (SINGLE OUTFLOW TRACT)[6]

Pulmonary atresia instead of pulmonary stenosis may form one of the elements of a tetralogy of Fallot Life is maintained (a) by a patent ductus arteriosus which carries blood from the aorta to a branch of the pulmonary artery distal to the atresia, or (b) through hugely dilated bronchial arteries which come off the dextroposed aorta An atrial septal defect is often present Extreme cyanosis is usual Attacks of dyspnea are common and may be fatal Syncopal attacks occur with exertion There may be no significant murmur or a loud systolic murmur in the pulmonic area or occasionally a continuous murmur The second 'pulmonic sound referred from the dextroposed aorta, is loud and clear, i e not split Inability to introduce the cardiac catheter into the pulmonary artery although it can be made to enter the dextroposed aorta, suggests the presence of pulmonary atresia Angiocardiography shows early opacification of the aorta of which the root may be displaced and the arch abnormally large There is an enlarged displaced ascending aorta and no main pulmonary artery which differs from the appearance in the usual Fallot s tetralogy Angiocardiography discloses whether pulmonary arteries are available for anastomoses There may be a distinctive vascular pattern characterized by coarse stippling of the hilar vascular markings when there are enlarged bronchial arteries, with absence of the hilar comma[79]

If the associated dextroposition of the aorta is not extreme and a rudimentary pulmonary vessel of sufficient size can be found the Blalock operation may be successful As a rule the operative mortality is very high largely because the patient s life depends on the collateral vessels and some of these are divided during the operation In addition the postatretic pulmonary artery is thin walled and poor for anastomosis Lillehei et al[55] reported the successful correction of a case of pulmonary atresia by intracardiac surgery under direct vision, using a donor for cross circulation The ventricular septal defect was closed, a new opening was created at the top of the outflow tract of the right ventricle and the pulmonary artery distal to the atresia was anastomosed to this newly created orifice

COMPLETE TRANSPOSITION OF THE GREAT VESSELS[18 11 233]

This is one of the leading causes of death from the cyanotic forms of congenital heart disease The aorta arises entirely from the right ventricle and the pulmonary artery from the left ventricle Thus unoxygenated blood from the peripheral veins reaches the right atrium and right ventricle and is thence pumped by way of the aorta into the general circulation without passing through the lungs Another circulation is formed by oxygenated blood flowing from the pulmonary veins left atrium and left ventricle into the pulmonary artery and through the lungs again Life depends on the degree of cross flow between these circulations by way of a patent ductus arteriosus in more than half of the cases by way of an interventricular septal defect in one third or by way of a patent foramen ovale or interatrial septal defect in the others In the majority of cases the aorta and pulmonary artery are of equal size in some the pulmonary artery is larger and occasionally the aorta has the greater diameter An anatomic problem, which is of importance if surgical correction is contemplated is the origin of the left coronary artery from a position close to the pulmonary artery Therefore, at least one coronary artery must be transplanted to arise from the aorta when the position of the great vessels is surgically restored

Transposition of the great vessels occurs at least two or three times as often in males as in females At present the outlook for life is ex

tremely grave since about 50 per cent of the infants die in the first month of life and the average age at death has been found to vary from 3 to 19 months.[41, 223] Because of this and because of the promise that an effective surgical repair may become available, diagnosis in the first months of life is especially important. However, a considerable number of children with this disturbance survive beyond the age of three, usually because there is a large ventricular septal defect permitting adequate mixing of blood from both sides of the circulation.

Clinical Features

Cyanosis is usually prominent from birth and is more intense than in Fallot's tetralogy. Characteristically, the cyanosis is intensified by crying and is incompletely relieved by oxygen. In cases of complete transposition with patent ductus arteriosus the cyanosis is said to be deeper in the upper than in the lower half of the body, since the more oxygenated blood in the left ventricle is transported by way of the transposed pulmonary artery and the patent ductus arteriosus to the descending aorta. However, this distinction in degree of cyanosis is either not mentioned or has been overlooked in most reported cases. Feeding is poor and weight gain inadequate. Dyspnea is common, usually in exertion, and may be associated with syncope of effort. Cough occurs in many but squatting is rare or absent. Polycythemia may appear after several months, but not clubbing unless the infant survives at least six months. Congestive heart failure, with distention of the cervical veins and hepatic enlargement, develops frequently.

In at least one third of the cases there are no murmurs. When present, the murmur is soft, systolic and located in the third left interspace, and occasionally it is accompanied by a thrill. It is most likely to occur when there is an associated ventricular septal defect. A pulmonary diastolic murmur is occasionally present. The second pulmonic sound is usually very loud in contrast with that in Fallot's tetralogy. Gallop rhythm is common. Cardiac enlargement is prominent and occurs regularly. The relatively normal cardiac size at birth, with rapid progressive enlargement even within the first three or four weeks of life, is diagnostic of complete transposition.

Roentgenologic Examination[4, 11]

The heart is enlarged and may be egg shaped with the narrow end at the apex. The left border may form a peculiar long bulge in its middle salient and show an aortic pulsation. But more often there is a concave left middle segment. A diagnostic feature, though present in only one third of the cases, is a narrow vascular pedicle. The peripheral pulmonary vessels are engorged and the pulmonary markings increased. When the lung fields appear oligemic in the presence of other evidence suggesting complete transposition, it is probable that there is a complicating pulmonic stenosis. The varied appearance in different cases limits the diagnostic value of roentgenologic examination in this disease.

Angiocardiography[59, 11, 104, 170] is usually necessary to make or confirm the diagnosis. The aorta fills promptly with dye and is seen to arise directly from the right ventricle. The aorta may be seen to form the left upper mediastinal border, lying in the usual position of the pulmonary artery and right ventricular outflow tract.

Electrocardiography usually shows evidence of right ventricular hypertrophy and tall P waves in lead II.

Cardiac Catheterization may be helpful in demonstrating other defects. The catheter may pass through an atrial or ventricular septal defect or occasionally into both the aorta and pulmonary artery. Pressure relationships and oxygen contents depend on the nature of the communication between the left and right sides of the circulation.

If the communication is by way of a ductus arteriosus, then the more oxygenated blood from the pulmonary artery (arising from the left ventricle) reaches the lower half of the body and the femoral arterial oxygen is higher than the brachial. Such patients may have a worse prognosis because the coronary arteries receive the less oxygenated blood from the ascending aorta.

Surgical Treatment

Blalock and Hanlon[41] attempted to improve the cross over of oxygenated blood (1) by an anastomosis of the right superior pulmonic vein to the right atrium, (2) by creating an interatrial septal defect and in addition anastomosing the proximal end of the subclavian artery to the distal end of the pulmonary artery. They reported improvement in

two thirds of the children who survived, but the mortality was high Experimental studies of surgical possibilities for treating complete transposition were reported by Lillehei and Varco[268] and by Bjork and Bouckaert[37] Mustard and associates[296] described a surgical method using a Cowan perfusion pump and a monkey lung as an oxygenator, which they employed in operation on seven infants none of whom survived Hypothermia and mechanical pump oxygenators have been employed Cross and associates[109] described a technique whereby external plastic shunts were used to by pass the circulation around the aortic and pulmonic valves and the proximal great vessels while repair of the great vessels or valves can be undertaken Murphy et al[94] reported that 7 of 32 infants or children operated on for transposition of the great vessels had survived and showed significant improvements after a follow up period of 15 to 36 months Baffes[15] described a new technique which utilized a homologous aortic graft to transpose the inferior vena cava to the left atrium while the right pulmonary veins were transposed to enter the right atrium This was satisfactorily applied in one case involving an infant who showed considerable improvement postoperatively

THE TAUSSIG BING SYNDROME[398, 271]

The aorta is completely transposed and arises from the right venticle and there is levoposition of a large pulmonary artery which overrides the left ventricle but does not arise completely from it The aorta is situated anteriorly the pulmonary artery posteriorly There are also a high ventricular septal defect and right ventricular hypertrophy The prognosis for life is fair and much better than with complete transposition

The syndrome is characterized by cyanosis from birth, underdevelopment dyspnea on exertion, cardiac enlargement systolic murmur in the left third intercostal space, loud second pulmonic sound, moderate polycythemia electrocardiographic evidence of right ventricular hypertrophy or incomplete bundle branch block, and large pulsating hilar vessels and increased pulmonary vascular markings on fluoroscopy

Angiocardiography shows that the aorta fills directly from the right ventricle but unlike its situation in complete transposition the pulmonary artery is seen to override both ventricles and fills simultaneously with the aorta Subsequent films show poor filling of the left ventricle and reopacification of the pulmonary artery On the basis of angiocardiography the diagnosis has been made in vivo and confirmed anatomically[284]

Cardiac catheterization[15] shows the catheter passing into the aorta from the right ventricle but also into the pulmonary artery The oxygen content is higher in the pulmonary artery than in the aorta Equality of pressures in the right ventricle, aorta and pulmonary artery indicates the presence of a large ventricular septal defect The syndrome is usually confused with the Eisenmenger complex, but in the latter cyanosis does not start at birth and catheterization studies do not show the oxygen content in the pulmonary artery higher than in the aorta

SINGLE VENTRICLE WITH PULMONARY STENOSIS[84]

These are cases in which the ventricular septum fails to develop normally and there is a single ventricle with one or two atrioventricular orifices The atrial septum may be intact but more often has a defect The clinical picture resembles that of the tetralogy of Fallot and like this syndrome it is amenable to surgery by the Blalock procedure

A single ventricle may be associated with mitral or tricuspid atresia or with transposition of the great vessels

PATENT DUCTUS ARTERIOSUS

Patent ductus arteriosus is important because it is one of the frequent clinically significant congenital cardiovascular lesions and because it is completely curable by surgery According to Abbott s[1] figures for autopsied cases, a patent ductus arteriosus occurred 150 times among 1000 cases of congenital heart disease of which 92 were uncomplicated, it was exceeded in frequency only by atrial and ventricular septal defects In the series of Wood et al[4-5] it was encountered as an isolated lesion in 12 5 per cent of their cases of congenital heart disease and was only exceeded in frequency by interatrial septal communications and slightly by isolated pulmonic stenosis Patent ductus arteriosus occurs about three times as frequently among females as among males[238, 50]

Embryology and Pathogenesis

The ductus arteriosus arises from the sixth left aortic arch and connects the main or left pulmonary artery with the descending arch of the aorta just below the origin of the left sub clavian artery at the termination of the so called isthmus of the aortic arch In fetal life the blood from the right atrium which comes from the superior vena cava and which does not pass through the foramen ovale is ex pelled into the right ventricle and the pul monary artery Almost all the blood from the pulmonary artery passes through the wide patent ductus arteriosus to the descending aorta and its branches to supply the lower half of the body Only a minute portion of the pulmonary arterial blood reaches the non functioning lungs

According to Patten [309] however the blood supply to the lungs increa es gradually in fetal life until shortly before birth a fair pulmonary circulation develops But it is only after birth when the lungs assume their respiratory func tion and their alveoli and the pulmonary vessels expand that the major quantity of blood from the main pulmonary artery tra verses the pulmonary circulation while less and less is shunted through the ductus ar teriosus It is uncertain whether the ductus ceases to function immediately after birth[21] or gradually after an interval of weeks [348] Ana tomic closure usually occurs by the end of the third month (in about 80 per cent of cases) and at the end of one year the ductus is ob literated in 95 per cent of cases Rarely closure has been reported to occur later in life [86] When the ductus closes it is converted into a fibrous cord known as the ligamentum arteriosum

Many theories have been offered to explain the mechanism of closure of the ductus ar teriosus The mechanical theory as indicated by Klotz [43] maintains that the ductus closes because of a fall in its blood pressure as the pulmonary arterial stream is deviated to the functioning lungs According to Klotz [243] when the blood pressure has fallen the extremely muscular walls obliterate the lumen by their tonic contraction and initiate the process of fibrosis On the other hand persistent patency of the ductus arteriosus results from the main tenance of a relatively high pressure in this canal According to the studies of Kennedy and Clark [36] the oxygen in the blood is the im portant factor in closure of the ductus ar teriosus

Pathology

From the standpoint of surgical manage ment it is important to recognize two groups, namely patent ductus arteriosus with as sociated cardiac anomalies and uncompli cated patent ductus Patent ductus ar teriosus with aorta to pulmonary artery shunt has been distinguished from patent ductus arteriosus with reversal of shunt (pulmonary artery to-aorta) due to pulmonary hyperten sion (p 769) Among the associated lesions are infantile coarctation of the aorta complete transposition of the great vessels pulmonary atresia or pulmonary stenosis [60] interatrial or interventricular septal defect In some of these cases patency of the ductus is essential to the maintenance of life

The patent ductus arteriosus usually forms a cylindrical tube of variable caliber and most often less than 1 cm long in the adult Or the communication may be of the window type in which there is merely a fistula between the aorta and pulmonary artery In such cases surgical ligation or section may be impossible The ductus is sometimes funnel shaped and wider at the aortic end it may be aneurysmal and its lumen filled with thrombus Rarely the pulmonic end is incompletely closed by a membrane

The pulmonary artery and its branches be come widened Rarely there may be an aneurysmal dilatation of the pulmonary artery Both ventricles are somewhat dilated and hypertrophied

Pathologic Physiology (See also Cardiac Catheterization p 768)

In uncomplicated patency of the ductus ar teriosus the higher pressure in the aorta shunts blood from that vessel into the pul monary artery during both systole and diastole Since the pulmonary artery receives blood from the aorta as well as from the right ventricle the pulmonary blood flow is above normal the vessel becomes dilated and its pulsations may be exaggerated

According to the measurements of Burwell Eppinger and Gross[59] the shunt was of great magnitude from 4 to 19 liters of blood flowing per minute from the high pre sure area in the aorta to the low pressure area in the pulmon ary artery The aortic pulmonary shunt also results in increased work for the left ventricle

According to Eppinger, Burwell and Gross[148] the cardiac output is two to four times normal Eppinger and his associates calculated that 45 to 75 per cent of the blood pumped by the left ventricle into the aorta is shunted through the ductus and lungs back to the left side of the heart without supplying the periphery of the body However the shunt is probably much less in many asymptomatic cases[160]

Dilatation and hypertrophy of the left ventricle are usually present although in most asymptomatic cases this is not demonstrable clinically On the other hand Eppinger and Burwell[148] observed a moderate degree of left ventricular enlargement roentgenographically in 8 of 9 patients who were operated upon for a patent ductus The presence and extent of left ventricular enlargement depend on the degree of left ventricular strain The leakage of blood from the aorta to the pulmonary artery is accompanied by a fall in diastolic pressure similar to that in cases of aortic regurgitation

In infants there may be a reversal of flow with a venous arterial shunt during crying sucking or coughing Such a reversal with transient or terminal cyanosis may occur also during pulmonary infections and heart failure A reversal of flow with cyanosis occurs also *when there are certain associated anomalies* such as complete transposition of the great vessels or whenever there is marked pulmonary hypertension (p 769)

The following clinical discussion applies to the cases of uncomplicated patency of the ductus arteriosus

Clinical Features

Symptoms In many if not most cases there are no symptoms due to the lesion Cyanosis is absent although it may occur rarely with pulmonary vascular disease and pulmonary hypertension (p 770) When symptoms appear they are most often exertional dyspnea and palpitation or fatigability Occasionally the subjects with a patent ductus are slender undersized and underdeveloped (habitus gracilis) and pale The underdevelopment is attributed to a diminished systemic arterial *blood supply as denoted anatomically by* hypoplasia of the aorta This results from the short circuit of a large portion of the aortic blood through the pulmonary circuit (supra) Cardiac failure develops sooner or later in most patients but it is emphasized that even in infancy or early childhood heart failure may be due to a patent ductus[229]

Physical Signs The physical signs are characteristic The pathognomonic sign is the *Gibson murmur*[175] which is variously described as continuous machinery like train in tunnel, humming top, churning sawing etc It is a long and rumbling murmur which occupies most of systole and diastole (Fig 134*D*) There is often an accentuation in late systole[203] The murmur may be diffuse but usually is localized or loudest in the second left interspace near the sternum the site of the dilated pulmonary artery Occasionally it may be heard in the third left interspace near the sternum The systolic element radiates to the cervical vessels and often posteriorly *A systolic thrill* is usually and a diastolic or continuous thrill is rarely palpable over the site of maximal intensity of the murmur

As a rule, if there is no continuous murmur, there is a rough long *systolic murmur* with maximum intensity in the second left interspace *near the sternum, or occasionally in the* first or third left interspace An increasing number of patients with patent ductus arteriosus are being seen who have no murmur or only a systolic murmur[314] As a rule such patients are either in congestive heart failure or have an associated pulmonary hypertension In infants only a systolic murmur is usually audible, although a machinery murmur may be heard in the first few months of life The presence and character of the murmur depend on the development of a significant shunt and the height of the aortic pulmonary artery pressure difference (gradient) In young infants the gradient may be very small or insignificant in diastole or both systole and diastole

Occasionally there is an apical diastolic murmur,[11] due to functional mitral or tricuspid stenosis (excessive blood flow) and there may be a diastolic murmur along the left border of the sternum due to pulmonary insufficiency

The *second pulmonic sound* is accentuated and may be reduplicated

Percussion may reveal a thin, rectangular area of dullness in the second and third left interspace (Gerhardt's dullness) overlying the dilated pulmonary artery This is inconstant or difficult to demonstrate by physical examination

When the ductus arteriosus is widely patent and there is a considerable arteriovenous shunt one often encounters the peripheral circulatory phenomena seen in cases of free aortic regurgitation (p 690) These result from the aortic regurgitation of blood into the pulmonary artery during diastole There is a *high pulse pressure* which may be due in part to an elevation of the systolic pressure but chiefly to a sharp drop in the diastolic pressure The diastolic pressure may fall sharply during exercise In addition to the high pulse pressure there may be a stenosis of the orifice of the left subclavian artery An infrequent sign is the *pulsus paradoxus*

Roentgenology

1 The size of the cardiac silhouette is usually normal when the shunt is small With large shunts there is an enlargement of the left ventricle and occasionally to a lesser extent of the right ventricle[230a]

2 The characteristic feature although not invariably present is a prominence of the pulmonary arc in the left upper portion of the cardiac silhouette[1 6] (Fig 134 A) This is known



Fig 134 Patent ductus arteriosus *A* Conventional posteroanterior view Prominent pulmonary artery segment

B Angiocardiogram Left oblique view Fusiform dilatation just beyond aortic isthmus where ductus is attached (arrow)

C Diagram of angiocardiogram

D Machinery type continuous systolic-diastolic murmur

Corrigan pulse *capillary pulsation* *Duroziez s sign* (pistol shot femorals) and other circulatory phenomena often associated with aortic insufficiency *Microplethysmography* usually discloses characteristic changes in the pulse wave of the finger, including blunting of the apex of the wave loss of differentiation between systolic rise and diastolic fall and loss of dicrotic notch[8] Occasionally the blood pressure is higher in the right arm than in the left and the *radial pulses are unequal* but this probably represents an associated coarctation of the aorta with as the x ray cap of Zinn The bulging cap of Zinn represents the dilated pulmonary artery In other cases the pulmonary artery is only slightly dilated and the pulmonary arc less conspicuous roentgenoscopically Prominence of the pulmonary artery with prominent pulmonary vascularity is observed also in cases of interatrial and interventricular septal defects but in the latter conditions there is right not left ventricular enlargement The post stenotic pulmonary artery enlargement in pulmonic stenosis is distinguished by the association of relatively avascular lung fields

3 Not only is the pulmonary arc prominent in most cases but its pulsation is considerably exaggerated The hilar shadows are also prominent both in size and pulsation These pulsations are rarely as striking and much less frequent than in cases of atrial septal defect

4 Increased fullness of the peripheral pulmonary vessels may be present if the shunt is of considerable size

5 There may be evidence of left ventricular and left atrial enlargement and this is especially frequent in infants

The enlargement of the pulmonary artery may be observed most readily in the right oblique view In the left anterior oblique view, a large ductus arteriosus may partially obscure the window of the aorta A valuable diagnostic sign, occasionally present is a calcified plaque near the caudal end of the arch of the aorta (i e the site of junction of the ductus and aorta)[344] in young persons in whom arteriosclerotic calcification of the aorta is otherwise rare

Angiocardiography is not usually of diagnostic importance It may reveal a localized dilatation of the descending aorta just beyond the isthmus (Fig 134*B* and *C*) In the early films the pulmonary artery shows weak contrast material presumably due to dilution by blood shunted from the aorta

Retrograde aortography (p 16) not only discloses simultaneous opacification of the aorta and pulmonary artery but also visualizes the ductus directly However the procedure is rarely indicated Sometimes patency of the ductus is indicated by prolonged or renewed visualization of the pulmonary artery after there is no longer any contrast medium in the right ventricle [31]

Electrocardiogram

The electrocardiogram is often normal There is generally no axis deviation These negative findings are important in differential diagnosis In infants there is commonly electrocardiographic as well as roentgenologic evidence of left ventricular hypertrophy As age increases left and right hypertrophy become balanced In cases with moderate pulmonary hypertension there may be evidence of both left and right ventricular hypertrophy Left ventricular hypertrophy may be associated with electrocardiographic changes of right bundle branch block

Cardiac Catheterization

The blood oxygen content is significantly higher in the pulmonary artery than in the right ventricle[116,117] (usually by more than 2 vols per cent)[illegible] The pulmonary arterial pressure and that in the right ventricle may be normal, or moderately or greatly elevated [illegible] Manometric studies in 24 cases showed a normal pulmonary artery pressure in 10, slight elevation in 6 and moderate elevation in 6, but not high enough to alter the left to-right (aortic to pulmonic) shunt[35] (p 770) In about one third of cases of patent ductus, the cardiac catheter may pass through the ductus [7] The pulmonary capillary flow exceeds that in the pulmonary artery, since the pulmonary capillaries also receive blood through the aortic pulmonary shunt

Diagnosis

The diagnosis of patent ductus arteriosus is based essentially on the presence of the typical machinery like murmur Confirmation is supplied by roentgenologic findings of a prominent pulmonary artery and especially by cardiac catheterization which reveals a higher oxygen concentration in the blood of the pulmonary artery than in that of the right ventricle and by passage of the catheter into the ductus in some cases Associated complicating lesions should be excluded

Course and Complications

Many patients never have symptoms referable to the patent ductus and die of independent causes Unfortunately the available statistics which are based on autopsied cases usually reported because of some special complication are misleading in so far as they are not likely to include the more favorable asymptomatic cases [30] According to Abbott[1] the average age at death is 24 years and according to Keys and Shapiro [231] 37 years, but some patients have a normal life span, and death has occurred at the age of 75 [157]

The commonest complications and causes of death are *congestive heart failure* and *bacterial arteritis or endocarditis* Other complications are less common Occasionally the dilated or even aneurysmal pulmonary artery or ductus arteriosus ruptures causing thoracic hemorrhage and death A dissecting aneurysm of the pulmonary artery may develop Thrombosis *of the ductus arteriosus* occasionally *leads to* pulmonary embolism Paradoxical embolism rarely results from the passage of thrombotic

material from the left atrium by way of the aorta and patent ductus to the lung. Occasionally there is hoarseness or aphonia due to paralysis of the left recurrent laryngeal nerve probably caused by the pressure of the dilated ductus arteriosus or pulmonary artery.[91]

Surgical Treatment

Surgical closure of the patent ductus corrects the abnormalities in circulatory dynamics, restores normal cardiac size, and eliminates the clinical symptoms and the risk of heart failure, bacterial endocarditis or other complications of a patent ductus.[194] Following operation the patient's hands and feet become warmer and the capacity for ordinary activity or physical exertion is increased. Patients with exertional dyspnea, palpitation, fatigability, weakness and chest pain are completely or almost completely relieved of these symptoms. Children who were malnourished and underdeveloped gain weight and improve in growth. The murmur and thrill disappear. The diastolic pressure rises and the pulse pressure falls. The heart rate is slowed as after the obliteration of other arteriovenous aneurysms (p. 694). The work of the heart as well as its size is diminished.

The technique of the operation has been described by Gross,[192] Potts,[315] Cade[71] and others. At first the ductus was closed by multiple ligatures, but recanalization occurred in about 10 per cent of cases. To avoid this Gross resorted to cutting the ductus and suturing the cut ends. Occasionally section of the ductus or even passing of ligatures cannot be performed because the ductus is too short. The mortality rate in uncomplicated cases should be well under 1 per cent. There are many short series of cases without a mortality. Potts[315] reported that there was no mortality in 250 consecutive surgical closures of the patent ductus arteriosus.

The most suitable time for operation is between the ages of 3 and 15. However operation may be necessary and successfully performed in infancy.[295] It may be performed in adults, but with greater difficulty than in children.

Indications for Operation. Prompt operation is indicated if there is evidence of a large circulatory shunt and cardiac strain as suggested by cardiac enlargement, pulmonary vascular engorgement and a high pulse pressure. It is indicated in patients with symptoms of diminished cardiac reserve, and with present or previous heart failure as soon as medical treatment for heart failure has accomplished as much as it can. It is indicated in cases of patent ductus with bacterial arteritis after the bacterial infection has been controlled by antibiotics or if a satisfactory clinical response cannot be obtained with antibiotics. Finally, because of the poor prognosis without operation, and with the operative risk minimized, I recommend that the operation should be performed as soon as convenient *on all children with a patent ductus*, as a prophylactic measure. Sometimes there is rewarding improvement postoperatively even when there were no apparent clinical symptoms preoperatively. Among adults with patent ductus, section or ligation should be performed only if there is evidence of cardiac strain or failure.

Ligation or section of the ductus arteriosus is contraindicated when this anomaly is associated with other congenital cardiac defects for which the ductus circulation is a compensation. This group can usually be distinguished by the presence of cyanosis and, if doubtful, with the aid of angiocardiography and intracardiac catheterization.

PATENT DUCTUS ARTERIOSUS WITH PULMONARY HYPERTENSION AND REVERSED SHUNT[81, 110, 215, 284, 427, 505]

In uncomplicated patency of the ductus arteriosus there is a flow of arterialized blood from the aorta to the low pressure pulmonary artery. When there is an associated pulmonary hypertension, which occurs in about 10 per cent of cases of patent ductus,[275] the pulmonary artery pressure may exceed that of the aorta and unoxygenated blood flows from the pulmonary artery to the aorta. The clinical picture in such cases differs strikingly from that of patent ductus, notably in the usual absence of the machinery murmur and in the presence of cyanosis.

Pathology

The right ventricle is hypertrophied. The pulmonary artery may be wider in diameter than the aorta. The ductus arteriosus is patent and usually large. The pulmonary arteries and arterioles may show no significant abnormality or they may present lesions of an occlusive nature.[81, 126] The arteriolar walls are thickened and their lumina narrowed or closed. The small muscular pul

monary arteries may disclose medial hypertrophy, increase of the elastica and subintimal fibrosis Medial hypertrophy and thrombosis of medium sized pulmonary arteries have been noted The possibility that the occlusions may be due to embolization is not excluded

Pathologic Physiology

The pressures in the pulmonary artery and systemic circulation are fairly equal in fetal life With the onset of pulmonary respiration at birth, the right ventricle pumps blood against the low resistance of the pulmonary vessels, in contrast with the left ventricle which works against the higher resistance of the systemic circulation Since the output from both ventricles is identical the pressure in the right ventricle and pulmonary artery is lower than that in the left ventricle and aorta If the ductus fails to close, the flow is from the higher pressure area in the aorta to the lower pressure area in the pulmonary artery If however, the pulmonary resistance is elevated at birth as a result of narrowing or occlusion of the small pulmonary arteries and arterioles there is no fall in resistance to right ventricular work with the onset of pulmonary respiration, and the pressure in the pulmonary artery does not fall normally If the pulmonary resistance and blood pressure remain higher than those in the systemic circulation the ductus arteriosus which normally closes as pulmonary arterial blood is detoured from it through the pulmonary vessels, now continues as an active channel because of the persistent high pressure in the pulmonary artery This hypothesis assumes that the patency of the ductus is actually secondary to the increased pulmonary resistance and pulmonary hypertension This is supported by the observation that cyanosis in these cases is present from birth If one regards the patency of the ductus and the pulmonary hypertension as due to two different mechanisms, then the pulmonary hypertension merely determines the direction of flow in a ductus which is patent for other reasons

Exertion tends to increase the pressure in the pulmonary artery relative to that in the aorta and thereby to increase the shunt of pulmonary (unoxygenated) blood through the ductus This probably results from the fall in systemic resistance as the blood flow increases with exercise On the other hand the increased blood flow cannot be handled by opening of vascular channels in the obstructed pulmonary vascular bed, hence the pulmonary resistance is unchanged or augmented as blood flow increases with exercise resulting in higher pulmonary blood pressure Sometimes the pulmonary artery pressure is elevated but is slightly less than aortic pressure at rest Under such circumstances, the pulmonary artery pressure may exceed that in the aorta only with exercise, and the reversal of flow may be intermittent [71]

The cause of the pulmonary hypertension in some cases or of the underlying vascular lesions in others is obscure

Clinical Features

The outstanding features are the cyanosis, usually present from birth, and dyspnea on exertion Squatting is present occasionally The cyanosis is increased with exercise and is distinctly more intense in the lower than in the upper half of the body and more in the left than in the right hand These local differences in intensity of cyanosis are accentuated by exercise The greater cyanosis in the lower half of the body is due to the fact that the head and upper extremities receive an oxygenated blood supply from the great vessels of the aortic arch, which come off before the site of the ductus On the other hand at the aortic end of the patent ductus, the oxygenated blood from the upper aorta becomes mixed with unoxygenated blood from the pulmonary artery and this relatively less oxygenated blood supplies the lower extremities But the left subclavian artery, which is close to or only a short distance above the ductus insertion in the aorta, receives some of this unoxygenated blood especially with exercise, and the left hand is more likely to appear cyanotic than the right

There is usually a loud systolic *murmur*, maximal in the third interspace along the left border of the sternum The murmur may be absent Occasionally there is a diastolic murmur along the left sternal border The second pulmonic sound is often accentuated and may be reduplicated

Roentgenologic Examination

The main pulmonary artery and the main pulmonary arterial branches are prominent and the former may show exaggerated pulsation The pulmonary fields are normally vascularized The right ventricle is enlarged (Fig 135*A*)

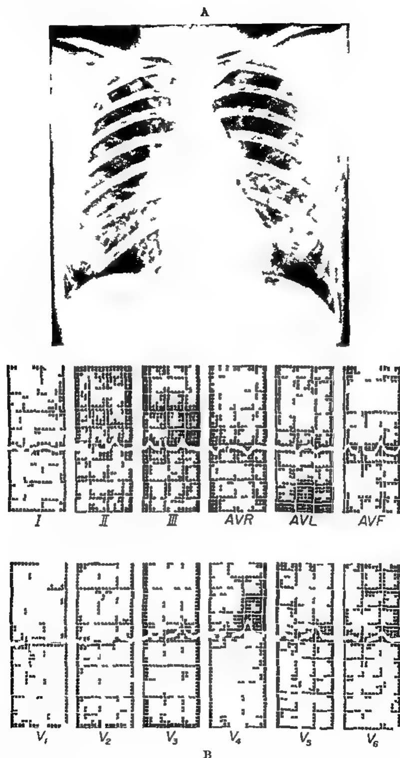


Fig 135 *A* Patent ductus arteriosus with pulmonary hypertension and reversed shunt Roentgenogram shows prominent pulmonary artery and increased vascularity of pulmonary fields

B Electrocardiogram shows right axis deviation vertical electrical axis but with insufficient evidence of right ventricular hypertrophy

Angiocardiography

A right-to left shunt through the ductus may be clearly indicated by visualization of the distal aorta simultaneously with the pulmonary artery while the ascending and transverse aorta are not yet visible Other sources for the shunt can be excluded by lack of visualization of the left cardiac chambers

Electrocardiogram (Fig 135*B*)

There is usually evidence suggesting right ventricular hypertrophy with tall R waves, ST segment depressions and T wave inversions in the right precordial leads Evidence of left ventricular hypertrophy is usually masked

Cardiac Catheterization Pressure Determinations and Oximetry

The catheter may enter the aorta by way of the pulmonary artery and patent ductus The pulmonary artery pressure is elevated and exceeds that in the systemic circulation Blood from the femoral artery shows an oxygen saturation considerably below normal, e g 60 to 70 per cent whereas that from the brachial artery is only moderately below normal saturation e g 90 per cent The pulmonary blood flow is normally or slightly diminished, whereas the maximal systemic flow (including the shunted blood) is two or three times as large

Diagnosis

Cyanosis frequently from birth the presence of a cardiac murmur and the localization of the cyanosis or of its greater intensity in the lower half of the body are clinically diagnostic The color of the left and right hands and of the right hand and right foot should be contrasted after exercise Arterial oxygen determinations of blood from the upper and lower extremities and findings on cardiac catheterization confirm the diagnosis and differentiate this from other forms of congenital heart disease with cyanosis

Prognosis

Patients may live for many years without heart failure although with moderate cyanosis

Treatment

Surgical closure in these cases appears to be contraindicated Usually such closure has resulted in a fairly prompt fatality[110, 268] Apparently the patent ductus serves as a compensatory safety valve for the right ventricle and its ligation is intolerable However in isolated cases the ductus has been successfully ligated[218, 3, 141b] In these the pressures in the pulmonary artery and aorta are about equal and reversal of flow occurs chiefly during exercise If ductal occlusion is contemplated at operation, it is important to occlude the ductus temporarily for 15 or 20 minutes and observe the pulmonary artery pressure If the pulmonary arterial pressure rises, the ductus should not be closed Antonius et al[8a] reported a case of patent ductus arteriosus with pulmonary hypertension and bidirectional shunt in which delayed closure was accomplished by partial ligation and wrapping with polyethylene sheeting

PERSISTENT TRUNCUS ARTERIOSUS COMMUNIS[99, 341]

Closely related to patency of the ductus arteriosus are the cases with a common arterial trunk, instead of distinct aorta and pulmonary artery, due to defective development of the bulbar septum There are two types (1) in the *true form of truncus arteriosus*, the trunk arises from both ventricles and gives off right and left pulmonary arteries from the ascending common trunk The pulmonary arteries are large and there is a good pulmonary blood flow (2) In *pseudotruncus arteriosus* there is no main pulmonary artery, there is atresia of the pulmonic valve, and the post atretic pulmonary artery is supplied with blood via a patent ductus, or more often bronchial arteries arising from the aorta supply the lungs with blood

If the pulmonary arteries arise directly from the truncus arteriosus, cyanosis is absent or minimal In the more frequent cases in which the circulation through the lungs is by way of dilated bronchial arteries cyanosis is usually intense as the pulmonary circulation and oxygenation are deficient There may be dyspnea In both types of cases there is often a harsh systolic murmur and thrill and cardiac enlargement but there may be no murmur The normal splitting of the second sound at the base is absent according to the phonocardiogram Death usually occurs early, but some patients reach adult life

Roentgen ray examination discloses a characteristic shelflike projection to the anterior chest wall in the left anterior oblique view a widened aortic shadow and absence of the contour of the pulmonary conus[111]

Angiocardiography shows the large common vascular trunk or a wide aorta arising *from* the right ventricle, but a similar picture may

be produced by pulmonary atresia The *electrocardiogram* usually shows right axis deviation, occasionally left axis deviation Postmortem examination discloses hypertrophy of both ventricles

If the pulmonary blood supply is by way of the bronchial arteries and a rudimentary pulmonary artery of sufficient size can be found, considerable clinical improvement results from anastomosis of a systemic artery (aorta innominate or subclavian) to the pulmonary artery (p 760)

A persistent truncus arteriosus is sometimes associated with a single ventricle [illegible] There may be a persistent left superior vena cava

AORTIC SEPTAL DEFECT—ANEURYSM OF SINUS OF VALSALVA

There is a small opening between the aorta and pulmonary artery about 1 cm above the semilunar valves [170, 15] The symptoms and signs may be insignificant or ill defined or may resemble those of a patent ductus arteriosus The diagnosis is suggested by finding all the manifestations of patent ductus, but the murmur is heard slightly lower and to the right of the site of the murmur in patent ductus Retrograde aortography has been used to make the diagnosis [168] The diagnosis was made by cardiac catheterization during life in two cases after study of films with the catheter in different positions in the aorta [319] Repair of an aortic septal defect has been reported [193]

In other cases the septum between the vessels is extremely thin leading to an aneurysm of the right sinus of Valsalva or more rarely of the posterior or left sinus [204, 159, 407, 59] Aneurysm of the sinus of Valsalva may be due to congenital disease of the aortic media sometimes associated with arachnodactyly (p 728) In a series of 15 cases of unruptured aortic sinus aneurysms reported by Steinberg and Finby [373] 6 were congenital (3 associated with arachnodactyly, 3 with coarctation of the aorta) and 9 were acquired and due to syphilitic aortitis or bacterial endocarditis These aneurysms may become clinically significant because of a tendency to perforation with a consequent defect between the right aortic sinus and the right ventricle (pulmonary conus) or pulmonary artery or between the posterior aortic sinus and the right atrium [illegible, 154] With perforation, the symptoms and signs resemble those of patency of the ductus but the murmur and thrill appear more superficial the murmur is situated lower (third or fourth left interspace) and there is more pronounced cardiac enlargement

The diagnosis is suggested by the sudden occurrence without apparent cause except exertion occasionally of symptoms of progressive heart failure and signs of a communication between the aorta and right side of the heart (continuous or harsh systolic murmur and thrill) In a personal case of sinus aneurysm with rupture into the right atrium, correctly diagnosed ante mortem, there were in addition to the sudden appearance of the murmur and thrill progressive congestive heart failure the development of right axis deviation not present in earlier electrocardiograms high pulse pressure and Corrigan pulse and a characteristic double pulsation in the cervical veins and over the liver At present the diagnosis of aortic sinus aneurysm is being made with increasing frequency, before rupture by means of angiocardiography [378] Surgical treatment of the ruptured aneurysm has been reported [63, 378]

Death may occur suddenly or within a few months or years but Abbott[1] has reported a case of survival for nine years after the perforation Bacterial endocarditis may complicate aortic septal defect or cause aneurysm of the sinus with rupture (p 868)

COARCTATION OF THE AORTA

Since Bonnet s[60] description, two forms of coarctation of the aorta are generally recognized the infantile and the adult As implied by these names the infantile form usually occurs in infants and is soon fatal while subjects with the adult form often reach mature life Exceptions occur in that the infantile form is encountered occasionally in adults and the adult form in subjects who die during infancy and childhood The *infantile form* is characterized by diffuse involvement of the aortic isthmus (from the origin of the left subclavian artery to the insertion of the ductus arteriosus with the constriction proximal to the isthmus) by the association of other congenital anomalies including a patent ductus and by cyanosis The *adult form* is characterized by a more localized constriction at or below the insertion of the ductus but distal to

the isthmus and left subclavian artery, by the absence of serious cardiac anomalies (except bicuspid aortic valve or subaortic stenosis), by a closed ductus, by a usually well developed collateral circulation and by the absence of cyanosis

Sex Incidence

There is a striking preponderance of males (4 to 1 or 5 to 1) among patients with coarctation of the aorta When it occurs in females, it may be associated with primary ovarian agenesis (Turner's syndrome)

Embryology and Pathology

The aorta in fetal life may be considered as divided into two functional units, the upper one extending from its cardiac origin to the insertion of the ductus at the lower end of the arch (i e, the isthmus) and a lower portion beginning at the insertion of the ductus and including the remainder of the descending aorta The upper unit receives the more oxygenated blood which, arriving in the right atrium from the placenta and inferior vena cava, is directed by the sinus valve through the foramen ovale to the left side of the heart and ascending aorta This oxygenated blood supplies the head the heart and the upper extremities Because this circuit contains only about half the venous return, it may be presumed that the aortic pressure is only sufficient to supply the upper unit and that the blood flow in this upper unit does not extend significantly beyond the isthmus The low pressure at the termination of the upper unit may account for the normal narrowing at the isthmus of the aorta

The unoxygenated blood from the superior vena cava, after relatively little mixing with the oxygenated blood in the right atrium is directed to the right ventricle, pulmonary artery and thence through the ductus arteriosus into the lower unit of the aorta This division of the circulation has been demonstrated roentgenographically in sheep fetuses after the injection of radiopaque material into the inferior and superior vena cava, respectively [1] Furthermore, the division into upper and lower units of the aorta may be an anatomic as well as a functional one, for there are cases in which the aortic arch and isthmus supplied by the left ventricle, are completely severed from the descending aorta beyond the isthmus, this unit receiving blood from the right ventricle through the ductus arteriosus [150]

Adult coarctation of the aorta, unlike the infantile form, is a late fetal or a neonatal anomaly [16] It occurs after and may be related to closure of the ductus arteriosus Normally an adequate pressure in the upper unit of the aorta prevents the constriction of the aorta at its ductal insertion when the ductus closes In instances of "adult" coarctation this constriction occurs because the aortic pressure in the upper unit is, at the time of ductus closure, insufficient to maintain the continuity between upper and lower aortic units This may be due to maldevelopment of the aortic valve and left ventricle as suggested by the frequent association of bicuspid aortic valve and subaortic stenosis

The *infantile type of coarctation is probably an early, primary developmental anomaly of the fourth left aortic arch,* occurring in the second month of fetal life Thus this lesion, unlike the usual adult type is associated with other developmental anomalies such as a septal defect or transposition of the arterial trunks Whatever the mechanism, the blood flow and pressure in the upper unit of the aorta is low leading to an exaggeration of the normally slight narrowing of the isthmus and to hypoplasia of the entire upper portion of the aorta Furthermore, owing to the associated cardiac anomalies or pulmonary vascular lesions,[137] there is often an elevated pulmonary pressure so that even when the lungs develop there is enough of a pulmonary pressure to keep the ductus open Hence patency of the ductus arteriosus almost always accompanies an infantile coarctation [354] Patent ductus arteriosus has been encountered in about 7 per cent of all cases of coarctation of the aorta which were treated surgically [108]

The *heart* reveals hypertrophy of the left ventricle in all cases The adult form of coarctation is not infrequently associated at necropsy with a bicuspid aortic valve which may be congenital or rheumatic (p 864) Congenital subaortic stenosis and aortic insufficiency occur occasionally in cases of adult coarctation, with or without bicuspid valves Miliary aneurysms of the small cerebral vessels are not infrequent especially at their bifurcation in the region of the circle of Willis Forbus[158] found the media of the vessels at the site of the aneurysm either very thin or absent The cerebral aneurysms may be due to the high tension in the upper half of the body (including the brain) which appears in

infancy as well as to a developmental defect Post stenotic aortic dilatation or aneurysm may occur just below the coarctation[255] Aneurysm of the aortic sinus may be associated with coarctation of the aorta[131]

Schwartz and Greene[352] described cases of coarctation of the aorta in children with involvement of the origin of the left subclavian An atypical form of coarctation of the aorta has been described in which the left subclavian artery is occluded but there is no obstruction of the blood flow in the thoracic aorta[47] Almost complete absence of the left radial pulse and a slow rise in pulse tracings were characteristic The diagnosis can be confirmed by angiocardiography

Pathologic Physiology in Adult Coarctation of the Aorta

There is a normal blood flow from the right side of the heart through the lungs and from the left ventricle into the aorta The blood flow to the head and upper extremities is normal or elevated[32] But because of the aortic constriction aortic blood to the lower half of the body is detoured A striking *collateral circulation* develops around the constriction in cases of adult coarctation[31] Branches of the subclavian artery above anastomose with branches of the descending aorta below the stenosis or occlusion The chief anastomoses are between (1) the superior intercostal branches of the subclavian artery and the first intercostal branches of the aorta within the thorax (2) the scapular branches of the subclavian artery and the aortic intercostal vessels in the chest wall (3) the internal mammary branches of the subclavian and the epigastric branches of the external iliac in the abdomen These anastomotic vessels become greatly dilated and the aortic intercostal vessels often erode the lower margins of the ribs posteriorly The collateral circulation may be limited to the interior of the chest wall and thus not visible or palpable clinically There are also mild cases of coarctation of the aorta with poorly developed collateral circulations

Detailed reviews of the anatomic and clinical features of coarctation of the aorta have been presented by Abbott[2] Blackford[25] King[233] Lewis[253] and Reifenstein et al[3]

Clinical Features

Symptoms are often absent The patient may be unaware of his disease until there is a sudden fatal complication such as rupture of the aorta or of a cerebral vessel or until cardiac failure or bacterial aortitis develops Certain symptoms may be associated with the hypertension which is usually present These include headaches dizziness tinnitus insomnia epistaxis and nervousness Neurologic symptoms may be the first manifestations due to cerebral complications (see below) The patient may complain of weakness coldness pallor *numbness or cramps in the legs due to* diminished circulation in the lower half of the body Occasionally there is intermittent claudication The temperature of the feet has been found diminished[■] *Symptoms of congestive heart failure* especially dyspnea may eventually result from the hypertension and left *ventricular enlargement* Occasionally there is palpitation and precordial distress Congestive heart failure commonly develops sooner or later But occasionally it occurs in infancy and coarctation must always be considered in the differential diagnosis of heart failure in infancy[17, 246a]

The *objective signs* are more striking and of diagnostic importance The subjects with adult coarctation are often robust muscular and intelligent There are striking bilateral supraclavicular pulsations due to large subclavian arteries Dilated tortuous *collateral vessels* may be visible or palpable Most often these are situated along the inner borders of and across the scapula in the axilla or less often along the sternum or in the epigastrium The vessels are more readily observed when the subject is in a warm room or has been active According to Campbell and Suzman[35] these collateral vessels are more readily observed if the patient leans forward Systolic bruits and thrills may be present over these dilated collateral vessels Cyanosis and clubbing are absent in the adult type of coarctation because there is no venous arterial shunt and the pulmonary blood flow ■ normal

Physical examination of the heart may reveal only a slight enlargement to the left and downward There is usually a moderately loud systolic murmur over the precordium most intense at the base but often heard also in the left interscapular region The murmur is occasionally loud and harsh and accompanied by a thrill Sometimes it is louder in the back than anteriorly The murmur may arise in the dilated collateral vessels or at the site of con

striction of the aorta There may also be murmurs of an associated subaortic or aortic stenosis and insufficiency

Arterial Pulses In contrast with the strong pulsations in the suprasternal and supraclavicular regions there is no palpable aortic pulsation in the abdomen The femoral pulses are weak or impalpable[384] The circuitous course of aortic blood flow to the femorals not only weakens the femoral pulse but also causes it to appear later than the radial pulse when simultaneous graphic records are made (Fig 136C) Normally the femoral pulse slightly precedes the radial

sure is considerably higher than the femoral systolic The arterial blood pressure in the upper and lower extremities has been measured directly by cannulization of the vessels and recorded by optical tracings[4 6 377 ...] These measurements revealed that whereas the systolic blood pressure was higher in the upper than in the lower extremity the diastolic pressures were equal or only slightly less in the lower than in the upper extremity The femoral systolic pressure was depressed but the femoral diastolic was usually slightly above normal From these observations Steele[377] concluded that the increased periph

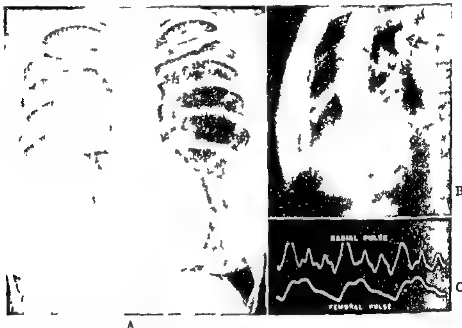


Fig 136 Coarctation of aorta *A* Notching of lower borders of ribs

B Angiocardiogram left lateral position Visualization of ascending aorta and arch At and beyond aortic isthmus irregularity and narrowing of aortic lumen (arrow)

C Simultaneous radial and femoral pulse to show delay of latter

Hypertension in Coarctation of the Aorta Hypertension is a characteristic feature of the adult type of aortic coarctation It may be absent if the anomaly is complicated by heart failure bacteremia and according to King[239] occasionally in uncomplicated cases The hypertension is chiefly systolic but the diastolic pressure may also be elevated to a variable degree *A diagnostic feature is the limitation of the hypertension to the upper extremities* the blood pressure in the lowers being normal or depressed Normally the systolic blood pressure in the femoral artery is about 20 mm higher than in the brachial In cases of adult coarctation the brachial systolic pres

eral resistance underlying the hypertension is generalized and involves lower as well as upper extremities However Bing and his associates[33] found the diastolic pressure elevated in the arms and not in the lower extremities and concluded that there was no *generalized* elevation of peripheral vascular resistance

Clinical studies of circulatory dynamics in cases of coarctation of the aorta[49] and animal experiments[305] have failed to elucidate the exact mechanism responsible for the hypertension and its limitation to the upper half of the body[204] The *mechanical theory* supposes that these abnormalities are purely the result of mechanical obstruction, ... but persistent

hypertension has not been produced experimentally in dogs by occluding the aortic isthmus at a level corresponding to the site of human adult coarctation The *humoral or renal theory* proposes that the hypertension is due to renal ischemia It is supported by studies of renal blood flow[164] and by the experiments in which hypertension in dogs[181] and in rabbits[345] was produced by means of constricting the aorta just above both renal arteries Hypertension did not follow similar obstruction below the origins of these vessels On the other hand the blood pressure in these experiments gradually fell to normal unless the aorta was clamped below as well as above the level of the renal vessels Studies by Scott et al [333] of experimental coarctation of the aorta favored a renal origin of the hypertension since transplantation of all functioning renal tissue above the site of the constriction caused a prompt reversion of the blood pressure to normal levels An observation which does not support the renal theory is supplied by a case reported by Maycock [79] in which there was pronounced brachial hypertension although the stenosis was below the level of the renal vessels The observations of Bing et al [37] (supra) and those of Hull[214] also indicate that the hypertension is not due to renal ischemia and a consequent humoral pressor substance but to the resistance of the aortic stenosis and the collateral vessels

Roentgenology

The heart is only slightly enlarged the enlargement involving the left ventricular contour as in cases of essential hypertension

The ascending aorta is dilated bulges somewhat to the right and shows increased pulsation

The aortic knob in the anteroposterior view is often small and may be absent and is in contrast with the prominent ascending aorta According to Fray [161] a pathognomonic feature is the presence of a localized defect or break in the continuity of the aortic arch on its convexity as viewed in the left anterior oblique view This break is situated at the junction of the transverse and descending portion of the arch and corresponds to the location of the coarctation at the point of insertion of the ligamentum arteriosum It is often difficult to outline the deformed and discontinuous descending aorta Gladnikoff[177] emphasized the recognition of a dilated left subclavian artery medial displacement of the aortic arch and indentation in the upper portion of the descending aorta as signs of coarctation

Attention has recently been directed to many accessory radiologic signs of coarctation of the aorta which have been neglected or insufficiently emphasized and which are of special diagnostic value in patients who have no rib notching [155] (1) Instead of a distinct aortic knob which is continuous laterally into the descending aorta the knob is small and indistinct and the transition to the descending aorta is vague and discontinuous [66] (2) There may be an indentation or concavity below the aortic knob at the site of coarctation (3) The descending aorta forms a lateral convexity below the aortic knob which simulates a second knob Occasionally this convexity is marked when it is the site of a post-stenotic aneurysm (4) The dilated left subclavian artery widens the left superior mediastinum which shows prominent pulsations The marked pulsations of the ascending aorta and left superior mediastinum contrast with the inconspicuous pulsations in the descending aorta (5) The internal mammary arteries may produce scalloped indentations in the anterior margins of the lungs suggesting multiple soft tissue masses especially in the left anterior oblique view [5 6] (6) In the lateral or left anterior oblique view an indentation in the posterosuperior aortic contour behind the tracheal air shadow denoting the coarctation site may be observed in 30 per cent of the cases [156]

Of at least equal diagnostic value and more readily discoverable is the *erosion of the lower borders of the ribs* by the large collateral vessels first noted roentgenoscopically by Roesler[321] and by Railsback and Dock[3 4] (Fig 136A) The erosions may involve a variable number of ribs from the third to the tenth usually on both sides and in their posterior portion The erosions are localized smooth and curvilinear They have been seen in patients aged 6 but as a rule do not become apparent before the age of 12[3 5] Since the collateral circulation and notching of the ribs should be well developed by the age of 13 to 14 absence of rib notching after that age is of surgical importance because it suggests that the collateral circulation is too poorly developed to allow the complete occlusion necessary for surgical repair or that the coarctation is too mild to require such repair

The normal curve of the barium filled esophagus may be absent and the esophagus, when viewed in the right anterior oblique position may be seen to be situated to the right of the aortic arch It is displaced anteriorly and to the right

Angiocardiography and Thoracic Aortography

These techniques show distinctly the site of occlusion or stenosis of the aorta and often its approximate length and caliber may be estimated (Fig 136B) Preoperative demonstration of the site and extent of the coarctation is of great importance to the surgeon and determines whether the lesion is amenable to surgical repair and whether grafting may be necessary It is likewise of value to depict the relation of the constriction to the subclavian artery At the same time angiocardiography may disclose the presence of associated congenital vascular lesions and the state of the collateral circulation particularly the size of the internal mammary arteries and the aortic branches proximal to the coarctation Nicolson[30] reported a case of coarctation of the aorta with arrested bacterial endocarditis in which a calcified mycotic aneurysm at the site of constriction was clearly filled by contrast medium *Thoracic aortography* has also been employed to demonstrate the coarctation (p 16) An F7 or F9 catheter is inserted through the upper part of the exposed radial artery into the subclavian artery or aortic arch and 50 cc of 70 per cent Diodrast rapidly injected while roentgen ray films are made The ulnar artery has also been used, or the injection may be made directly into the left common carotid artery

Electrocardiography

This is not diagnostic There may be a left axis deviation In young infants there may be a pattern of right ventricular hypertrophy or right bundle branch block[430]

Ballistocardiography

The ballistocardiogram shows an absence of the K wave (p 61) which is restored following successful operation[6, 301] This is diagnostic if other causes of obstruction of the lower end of the aorta can be excluded

Diagnosis

The diagnosis of coarctation of the aorta is discussed independently of the general diagnosis of congenital heart disease because the disease is often masked as essential or malignant hypertension neurologic disease or cardiac failure without suggesting the possibility of a congenital cardiac abnormality Therefore the finding of hypertension, particularly in a young adult or child, should always be followed by palpation of the femoral pulse and determination of the femoral blood pressure If the femoral pulse is weak or absent and the blood pressure less than in the upper extremity, a tentative diagnosis of coarctation of the aorta is warranted[384] Confirmatory signs are then sought e g, visible or palpable collateral vessels over the scapular and interscapular regions, the axilla, parasternal or lower anterior chest wall murmurs or thrills in these areas, particularly a systolic murmur which is as loud or louder in the interscapular region as over the precordium roentgenologic observation of erosion of the ribs or defect in the aortic arch Eisenberg[140] emphasizes the fact that in children with the adult form of coarctation, there may be no great collateral circulation and no erosion of the ribs Diagnosis in such cases depends essentially on the difference in brachial and femoral blood pressures on weakness or absence of the femoral pulse and on confirmation by angiocardiography Unfortunately only a small portion of the cases of coarctation of the aorta are diagnosed *before the age of 15,* the optimal time of operation is below that age when the blood vessels are still elastic and irreversible cardiovascular damage has not yet occurred as a rule

Coarctation of the aorta should also be considered in cases of cerebral accidents in young persons

Occasionally a loud interscapular murmur or the presence of large collateral vessels suggests the diagnosis of coarctation in the rare cases of coarctation without hypertension

A simultaneous recording of femoral and radial pulse waves revealing a lag in the former, and delayed build up of the femoral pulse also confirm coarctation of the aorta[55, 4, 6]

The finding of unequal radial pulses with weakness or absence of the left brachial and radial, should suggest the possibility of aortic coarctation The latter should also be sought in cases of congenital subaortic stenosis

Prognosis Complications and Cause of Death

A knowledge of the outlook for untreated cases of coarctation has assumed increased importance since a technique of surgical treatment has been developed

The adult form of coarctation is occasionally compatible not only with long life[3,4] (Reynaud's patient lived to the age of 92) but often also with normal physical activity. Nevertheless, in reported series of cases death occurred at a relatively early age and in most instances before the fortieth year.[2] In Blackford's[39] series of 323 cases only 68 patients survived the age of 40, 125 died in the first year, 142 (including the former 125) died in the first decade and 112 between the ages of 16 and 40. This series included cases of the infantile as well as of the adult form of coarctation. In a more recent study of 104 cases of the adult type of coarctation of the aorta 61 per cent died during or before the fortieth year of life and the average age at death was 35.[3] But about 25 per cent of the patients attained a relatively normal life span and died of incidental causes. It is probable that these series include the most severe cases of coarctation and that those with the least disability and complications and with the longest life are either overlooked or treated by the general practitioner, the latter therefore frequently do not enter into hospital and autopsy statistics. Nevertheless the over all outlook for a normal life appears to be poor.

The commonest *complications* and *causes of death* are congestive heart failure, bacterial endocarditis or aortitis, rupture of the aorta and cerebral hemorrhage (exclusive of that due to bacterial emboli sm). About one quarter of the patients succumb from aortic rupture, one quarter from bacterial endocarditis and one quarter from complications of hypertension, i.e., either heart failure or intracranial hemorrhage.[195]

Progressive cardiac failure occurred in 25 per cent of Abbott's[2] 200 cases and sudden cardiac death in 8 per cent. Aside from hypertension, congenital subaortic stenosis, rheumatic cardiovalvular disease, coronary atherosclerosis and myocardial infarction are contributory factors in the development of the heart failure.

Rupture of the aorta was the cause of death in 23 per cent of cases in the series of Reifenstein et al.[277] This appears as a linear or zigzag tear usually 1 to 4 cm. above the aortic valve or just below the site of the coarctation. Microscopic examination of the ascending aorta reveals defects, splitting and disorientation of the elastic tissue in the media possibly due to prolonged mechanical stress. The upper aortic rupture produces a dissecting aneurysm of the descending aorta which may rupture into the pericardium and cause fatal cardiac tamponade. Rupture at the lower site is into a bronchus, esophagus or left pleural cavity.

Cerebral accidents are responsible for death in 10 to 17 per cent of reported series of cases. Subarachnoid or cerebral hemorrhage results from perforation of cerebral miliary aneurysms probably of congenital origin. Hemorrhage and encephalomalacia may also be caused by mycotic emboli and aneurysms of the cerebral vessels secondary to a bacterial endocarditis or aortitis. Headache, convulsions, hemiplegia, coldness and numbness in the lower extremities, vertigo, tinnitus and transitory visual disturbances are among the more common neurologic manifestations of coarctation of the aorta.[4,3] In some cases a minute perforation of a cerebral miliary aneurysm with intermittent leakage of blood has been diagnosed on the basis of recurrent apoplectiform seizures occurring suddenly, associated with severe bursting headache and followed by transient neurologic signs.[114]

Bacterial endocarditis most commonly involves the aortic valve which is often bicuspid, or the site of congenital or rheumatic stenosis and insufficiency. A similar clinical picture results from a *bacterial aortitis* in which the bacterial vegetations are situated in the aortic intima just below the site of the coarctation or occasionally in the ascending aorta.

Surgical Treatment

Successful correction of coarctation of the aorta was first accomplished independently by Crafoord and Nylin[106] and by Gross and Hufnagel.[168] There were 15 fatalities in the first 100 and only 2 deaths in the last 100 of 270 patients operated for coarctation of the aorta by Gross.[195] Clagett et al.[95] reported a mortality of 5.6 per cent among 177 operated cases, including many that were complicated, with patients as young as 2 weeks and many over 30 and up to 50 years of age. After the application of special clamps above and below the constricted portion of the aorta, the latter is resected and the continuity of the artery reestablished by end-to-end anastomosis. A continuous mattress silk suture with an everting type of repair is less apt to cause later aortic dissection than an anatomic

layer to layer anastomosis In children, interrupted silk sutures are employed to permit enlargement of the aorta with growth of the child Often the third pair of intercostal arteries must be sacrificed by careful ligation and section Care must be taken in the dissection especially below the coarctation, not to injure the thin walled intercostal arteries and thus cause massive hemorrhage After the anastomosis has been effected, the clamps on the aorta and subclavian artery must be removed gradually in order to prevent sudden flooding of the vascular bed and acute cardiac dilatation There is a rapid reduction in the hypertension in a few days or a more gradual reduction within three weeks after the operation Simultaneously there is a restoration of normal pulsations in the lower extremities Preoperative headaches epistaxis or leg cramps usually disappear after the operation

Many complicating factors may cause a modification of the technique of transection and end to-end anastomosis [94] When it is not feasible the large left subclavian artery may be sectioned its distal portion ligated and its proximal end anastomosed with the aorta which has previously been sectioned distal to the coarctation [363, 174] In a variable number of cases in which simple resection and anastomosis are technically difficult or impossible, continuity of the resected aortic coarctation is reestablished by the use of homografts [187] Freeze dried arterial homografts saved in graft banks have been found suitable [347] Long term observations have shown no dilatation or aneurysm formation in the grafts but calcification has been observed roentgenologically [98] Tubes constructed from Vinyon N cloth a plastic have also been employed to bridge arterial defects [40] In inserting aortic grafts above the level of the renal arteries there is always the problem of the brief time that the aorta may be occluded Johnson et al [2 0] described a method for maintaining an adequate blood flow through the thoracic aorta while inserting the graft by use of a glass or plastic tube with flanges around each end The graft is placed around the tube the aorta is clamped off the appropriate area is resected and the tube is tied into one and then the other end of the resected aorta Blood flow is reestablished and the graft sewn with the tube in place The tube is removed just before suturing is completed Julian et al [5] used induced hypotension and hypothermia for resection of coarctation of the aorta in cases requiring grafts

Other problems arise in connection with the persistence of a patent ductus [219, 103] with pulmonary hypertension, in combination with coarctation of the aorta The aortic constriction should be repaired without, as a rule, occluding the ductus There may be multiple sites of constriction [135] abnormalities in the vessels of the aortic arch, and aneurysms of the aortic wall or intercostal arteries or diffuse hypoplasia of the aorta Fatalities have occurred postoperatively in cases with associated mitral stenosis or severe aortic insufficiency

Indication for Surgical Treatment In view of the poor prognosis for unoperated coarctation of the aorta, and the relatively low operative mortality which should be less than 5 per cent, surgical treatment should be undertaken in virtually all patients whose general condition permits Cardiac failure is no contraindication although a brief time may be spent in an effort to control the heart failure medically before undertaking the operation Often, and especially in infants and young children, it is heart failure which is the indication for operation, and compensation can not be restored by medical measures until the coarctation is repaired surgically

The optimum time of operation is between the ages of 10 and 15 or 10 and 20, but it should be done at any time before 10 or even in young infants[288] if progressive cardiac enlargement recurrent heart failure or other serious disturbances forbid delay In such cases it is undesirable to wait until growth is completed before performing the operation for fear that the site of anastomosis will not enlarge with the remainder of the aorta In a person beyond the age of 20 vascular elasticity diminishes and aortic atherosclerosis may be of sufficient degree to impair the ease and safety of surgical manipulation Nevertheless, age, even up to 50 or beyond, is no absolute contraindication, successful anastomoses with gratifying clinical results have been attained

OTHER CONGENITAL CARDIAC ANOMALIES

RIGHT SIDED OR DOUBLE AORTIC ARCH

Embryology and Pathology

In the five week embryo there are six pairs of aortic arches connecting the primitive ventral and dorsal aorta The first two disappear but their ventral roots form the external carotid arteries The third arches form part of the internal carotid arteries The right fourth arch normally disappears but its ventral root forms the innominate artery The left fourth arch forms the arch of the adult aorta The fifth arches disappear The sixth arches also disappear but the ventral root on the right forms the pulmonary artery and the dorsal root on the left forms the ductus arteriosus

A persistent right sided aortic arch is found when the fourth left arch disappears while the fourth right embryonic arch develops into the adult arch of the aorta [29] In cases of right aortic arch the ascending aorta lies normally at its origin but then instead of arching upward and to the left across the front of the trachea, as it does normally it ascends and turns posteriorly to the right of the trachea and esophagus and then descends in one of two ways (1) The descending aorta is on the right of the trachea and esophagus or (2) it starts by passing from right to left across the right bronchus behind the trachea and esophagus and descends as a left aorta The aorta crosses to the left when it is drawn over by a ductus arteriosus or a left subclavian artery which arises in its normal left sided pattern

The right sided aortic arch occurs most often in association with the tetralogy of Fallot and other conditions in which there is dextroposition of the aorta It is seen more commonly in males

Occasionally both fourth arches persist and give rise to a double aortic arch encircling the trachea and esophagus [9] one passing in front and to the left of the trachea the other to the right of the trachea and esophagus The two limbs then join to form the descending aorta which is usually on the left side of the spinal column The space between the two arches is so small that the trachea and esophagus are compressed

Clinical Features

As a rule a persistent right aortic arch or less often a double aortic arch is clinically insignificant and is discovered accidentally by roentgen ray examination or at autopsy But they may become of clinical importance in three ways

First they occasionally produce symptoms, such as *dysphagia and dyspnea*, by compression of the esophagus or trachea at about the level of the third dorsal vertebra (dysphagia lusoria) These abnormal vascular structures are sometimes termed "vascular rings since they encircle the trachea and esophagus The trachea is particularly compressed by the double aortic arch with resulting respiratory distress and pulmonary infections Respiratory difficulty is likely to be intensified during or immediately after swallowing There may be wheezing respiration ("crowing stridor") due to tracheal obstruction A double aortic arch may itself produce a constricting vascular ring A right aortic arch may cause some bronchial compression but cannot alone produce compression of the trachea and esophagus However it is frequently associated with other structures such as a diverticulum formed from the vestige of the fourth left arch, or a left subclavian artery arising abnormally from a persistent right aortic arch or a ductus botalli which runs behind the esophagus or a right subclavian artery arising abnormally from the left descending arch any one of which helps to complete a constricting ring The term *arteria lusoria* has been applied to these abnormally situated vessels which may cause dysphagia In the cases in which the descending aorta crosses to the left attacks of croup and pulmonary infections are common in infancy and early childhood and brassy cough may result from compression of the left recurrent laryngeal nerve Noisy stridulous breathing mild dysphagia chronic cough and recurrent pulmonary infections are not infrequent in the cases in which a double aortic arch together with an aberrant left subclavian or patent ductus or ligamentum arteriosum forms a vascular ring around the trachea and esophagus [395] The onset of symptoms is usually later and the symptoms are usually less severe with

right aortic arch than with a double aortic arch

Second, the right sided aortic arch, especially when associated with pressure symptoms, has been diagnosed incorrectly as a mediastinal tumor lymphoma or aneurysm leading to the unwarranted administration of radiotherapy or to surgery

Third the possibility of these vascular anomalies and the close relationship of these aberrant vessels to the trachea and esophagus must be borne in mind when bronchoscopy or esophagoscopy is considered or when surgical correction of tetralogy of Fallot is contemplated

The *diagnosis* is made by *roentgen ray examination* (Fig 137) There is a pulsating shadow of the right aortic arch along the right border of the upper sternum and trachea extending to the right sternoclavicular joint On the other hand the aortic knob on the left is either missing or in cases of double aortic arch the left knob is small The trachea is slightly displaced to the left and in lateral views is seen to be narrowed in the lower segment During inspiration the lungs may not become completely aerated whereas in expiration they are hyperaerated indicating tracheal obstruction The barium filled esophagus is seen to be distinctly displaced to the left and indented This displacement distinguishes cases of right aortic arch from coarctation of the aorta and other congenital cardiac lesions associated with a small or absent aortic knob

In cases of right aortic arch with left descending aorta the barium filled esophagus is displaced forward and is characteristically kinked (Fig 137*B*) In double aortic arch, lateral films may show narrowing of the lumen and anterior displacement of the trachea, and indentation of the posterior wall of the barium filled esophagus

Angiocardiography portrays clearly the anatomic abnormalities of the aortic arch

The diagnosis of a compressing vascular ring should be suspected in any infant with stridor, cough or dysphagia and frequent respiratory infections



Fig 137 Right aortic arch *A* Posteroanterior view Absence of aortic knob on left A shadow is seen extending along right side in supracardiac area and caudad to right of spine (arrow) *B* Right lateral view Barium filled esophagus displaced anteriorly by right aortic arch

Treatment

Relief of the compression symptoms caused by a vascular ring of a double aortic arch has been effected by severance of the smaller aortic arch which is usually anterior Sometimes the ligamentum arteriosum is sectioned at the same time if it retrodisplaces the pulmonary artery Of 26 infants and children operated for a double aortic arch 21 survived and experienced extraordinary relief of symptoms [196]

In cases of right aortic arch the ligamentum arteriosum is sectioned in order to break the constricting ring and any other structures (e g a displaced left subclavian artery) or bands of tissue which contribute to the constriction must be cut The arch itself cannot of

course, be restored to a normal position Of 18 patients between 2 months and 12 years of age operated on for right aortic arch, there were no deaths and striking improvement in all[196]

OTHER ANOMALIES OF THE AORTIC ARCH

Aberrant Right Subclavian Artery

An aberrant right subclavian artery arising as the last branch of the arch of the aorta instead of normally from the innominate artery is a fairly frequent congenital anomaly It arises from the upper or medial aspect of the normal left sided aortic arch or it may arise at the junction of the arch and descending aorta It is frequently dilated at its origin or associated with an aortic diverticulum To reach the right arm the artery must cross the midline from left to right usually behind the esophagus occasionally between esophagus and trachea or rarely in front of the trachea

This partial "vascular ring" causes an oblique filling defect in the posterior esophageal wall at the level of the third or fourth thoracic vertebra which is demonstrable radiologically in the posterior anterior projection Or it causes a semicircular impression on the posterior esophageal wall and narrowing of the esophageal lumen, as seen in the lateral view This anomaly may be associated with other congenital cardiac lesions and was associated with tetralogy of Fallot in 4 of the 7 cases of Pattinson[310]

Although the aberrant right subclavian artery often produces no important symptoms it may cause such a delay in swallowing that feeding and nutrition are impaired Dyspnea is not a complaint but aspiration of food may occur Symptoms may not appear until late adult life[308] When significant disability is present, the anomalous subclavian artery can be freed from its bed doubly ligated and divided In a series of 12 such cases operated on by Gross[198] all patients survived and were freed of their dysphagia

Anomalous Innominate Artery

A leftward displacement of the origin of the innominate artery from the aorta may necessitate its passing anterior to the trachea with consequent tracheal compression Rarely it causes severe respiratory distress with stridor unrelated to feeding Roentgenologic examination in the lateral view shows an oblique indentation with narrowing of the anterior wall of the trachea The compression can be relieved surgically by tension sutures through the sternum raising the first part of the innominate artery and accompanying aortic arch anteriorly, and away from the trachea[196]

Anomalous Left Common Carotid Artery

Rarely this vessel arises from the aorta to the right of its normal position and compresses the anterior surface of the trachea as it courses upward and to the left toward the left side of the neck Roentgenologic examination in the lateral view discloses compression of the anterior wall of the trachea If this causes disturbing symptoms the first part of the carotid artery and accompanying arch is raised off the trachea by mattress tension sutures through the vessels and the sternum

Idiopathic Dilatation of the Pulmonary Artery

Dilatation of the pulmonary artery has been described in a variety of congenital cardiac anomalies with left-to-right shunts and in pulmonary stenosis with post-stenotic dilatation Occasionally dilatation of the pulmonary artery is observed and no other causative abnormality can be discovered The term "idiopathic" dilatation of the pulmonary artery has been applied to such cases[296, 401] The diagnosis is based on roentgenologic observation of a large pulmonary artery occasional prominence of the major branches, but normal vascularity of the peripheral lung fields and normal cardiac silhouette Other causes are excluded by the absence of clinical symptoms normal electrocardiograms and normal findings in cardiac catheterization Occasionally dyspnea on exertion and inconstant systolic murmurs and thrills have been reported

DEXTROCARDIA

Rarely the heart is situated outside the thoracic cavity, either in the abdomen or even outside the chest wall This is termed ectopia cordis The condition is almost always fatal in a few days or in a month or so Occasionally patients with ectopia cordis abdominalis survive into adult life Pectoral ectopia cordis through a fissure in the lower sternum permits viability if both pericardial layers are intact

Dextrocardia with Situs Inversus (Type I Dextrocardia)

True dextrocardia consists of a mirror like transposition of the heart so that the left chambers and apex are on the right and the

right chambers are on the left the apex being formed by the left ventricle There is a similar mirror like transposition of the other viscera (situs inversus), the spleen being on the right and the liver on the left There are no symptoms the condition is without clinical significance except in so far as it may complicate abdominal diagnosis However, there appears to be an increased incidence of severe bronchiectasis and sinusitis in cases of dextrocardia and situs inversus The association of situs inversus sinusitis and bronchiectasis is known as *Kartagener s triad or syndrome* [229, 191] There may be other congenital cardiac anomalies in cases of true dextrocardia

True dextrocardia with situs inversus may be recognized by physical examination, roentgenologically and by the electrocardiogram

Physical examination discloses the apical impulse on the right hepatic dullness on the left and the tympany of Traube s space on the right

Roentgen ray examination reveals the heart chiefly in the right chest with a mirror transposition of the silhouette so that the anterior view of the chest resembles the normal posterior view The stomach bubble is on the right side and the right leaf of the diaphragm is lower than the left

In the electrocardiogram lead I is a mirror image of the normal lead I, the P QRS and T waves are all inverted Lead II is identical with the usual lead III and lead III with the usual lead II If the leads to the arms are reversed, a normal electrocardiogram is obtained For this reason, whenever the electrocardiogram is that of dextrocardia it should be repeated to be sure that it was not due to improper connection of the leads Special problems arise in the interpretations of electrocardiograms when coronary occlusion or other cardiac disturbances are associated with situs inversus [361]

Isolated Dextrocardia (Type II Dextrocardia)

Occasionally there is an *isolated true dextrocardia*, with mirror image arrangement of the cardiac cavities the abdominal viscera retaining their usual position [343] This form of dextrocardia is almost always accompanied by other cardiac anomalies which may be of a serious nature e g especially cor triloculare biatrium but also pulmonary stenosis or atresia, and other conditions which produce persistent cyanosis A persistent left aortic arch is often associated In cases of isolated dextrocardia the P wave in lead I is usually upright, in contrast with its inversion in true dextrocardia with situs inversus [illegible] Isolated dextrocardia is occasionally associated with transposition of the aorta and pulmonary artery (dextrocardia with corrected transposition)

Corrected (False) Dextrocardia (Dextroversion of the Heart Type III Dextrocardia)

There are also cases of false congenital dextrocardia in which there is no mirror transposition the heart being merely displaced and rotated so that it lies in the right side of the chest But the left chambers are on the left and the right chambers are on the right and posterior There is usually an inverted T_1 and often a deep Q_2 or Q_3 but these may be modified by the effects of associated anomalies There are almost always serious associated cardiac anomalies which determine the clinical course, e g, pentalogy of Fallot, transposition of the great vessels pulmonary atresia, right sided aortic arch and defects or absence of the cardiac septa (cor biloculare) There may also be extracardiac anomalies such as congenital defects of the ribs or pectoral muscles or herniation of the lungs But Welsh and Felson[418] reported 6 cases of dextroversion of the heart without complicating anomalies

Dextroposition of the Heart (Secondary Dextrocardia Type IV Dextrocardia)

These are terms applied sometime to cases in which the heart is displaced into the right chest by some external and usually acquired disease of the lungs, pleura or diaphragm [211] There is no change in the electrocardiogram of lead I

Levocardia[1,4, 291, 350] denotes that the heart is normally on the left side but there is situs inversus of the other viscera As a rule there are associated cardiac anomalies, especially tetralogy of Fallot and interatrial septal defects ventricular septal defects, anomalies of the vena cava

CONGENITAL IDIOPATHIC HYPERTROPHY

Congenital idiopathic hypertrophy[339] includes a variety of different conditions which are gradually being segregated They have in common unexplained cardiac enlargement, usually absence of murmurs absence of cyanosis and often absence of any symptoms until



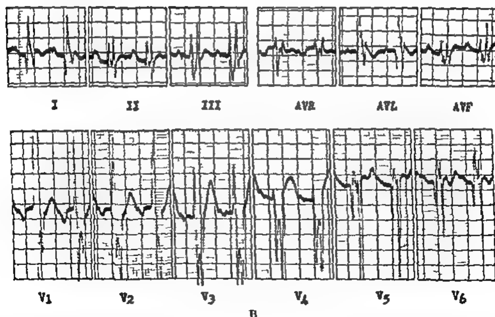


Fig 138 Idiopathic hypertrophy of the heart in an asymptomatic 26 year old man No murmurs Died suddenly six months later *A* Posteroanterior and right anterior oblique roentgenograms of the chest

B Electrocardiogram in above case Severe intraventricular conduction defect Q waves in leads I, aVL, V_1–V_6 suggesting anterolateral infarction

the patient develops heart failure a relatively short period before death

Congenital idiopathic hypertrophy includes cases of (1) endocardial fibroelastosis, (2) aberrant left coronary artery arising from the pulmonary artery, (3) glycogen storage disease of the heart, (4) rhabdomyoma, (5) interstitial (isolated, Fiedler's) myocarditis and (6) coronary artery lesions

1 Endocardial fibroelastosis[100, 401, 120, 151, 409, 234] is characterized by a gray, opaque thickening of the endocardium of one or more chambers the thickened areas being composed of layers of fibrous and elastic tissue There is little or no cellular infiltration The involved chambers are enlarged, usually the left ventricle and left atrium and the heart as a whole are two to four times normal size It is questionable whether the fibroelastosis is the primary cause of the cardiac hypertrophy or whether it is a nonspecific development in cardiac hypertrophy and failure of varied etiology There are commonly associated anomalies such as a tricuspid aortic valve, aortic stenosis, hypoplasia of the aorta or infantile type of coarctation of the aorta[235] Fibroelastosis may implicate the mitral valve and cause mitral insufficiency[234] There may be a family history of congenital heart disease Fibroelastosis occurs in adults[165b]

Symptoms, usually starting a month or two before death, include dyspnea, tachycardia and failure to gain weight There are generalized cardiac enlargement, hepatomegaly and electrocardiographic changes suggesting left ventricular hypertrophy Death is usually due to progressive congestive heart failure Treatment includes measures to control heart failure and improve nutrition and the use of antibiotics

2 Aberrant left coronary artery arising from the pulmonary artery is described below on p 791 It is distinguished by the electrocardiogram, which indicates anterior wall infarction (Fig 138)

3 Glycogen storage disease of the heart[92, 121] **(Glycogen cardiomegaly)**

Cardiac enlargement is due to abnormal storage of glycogen in the heart There is also some abnormal glycogen storage in the liver and skeletal muscle But this condition appears to be independent of if not unrelated to von Gierke s disease with its extreme glycogen accumulation in the liver and other organs, hepatomegaly, morning ketonuria, fasting hypoglycemia, etc , all of which are absent in glycogen cardiomegaly The heart is greatly enlarged, the left ventricle more so than the right The myocardial cells are swollen and contain a central nucleus surrounded by a large vacuolated area which stains for glycogen

Symptoms start in the first few months of life, and death usually occurs within six months, although glycogen cardiomegaly has been found in older children and also in adults Poor feeding, listlessness and poor weight gain progressive and eventually intense dyspnea and tachycardia are the outstanding manifestations Roentgen ray examination shows a large globular heart with occasional dorsally compressed trachea and esophagus, and atelectasis of the left lower lobe of the lung

The *electrocardiogram* is often distinctive and shows left axis deviation *deeply depressed ST segments in the standard leads and left precordial leads,* T inverted in all standard and left precordial leads and occasional ST segment elevation in V_1

The *diagnosis* should be suspected whenever there is "idiopathic" cardiac hypertrophy with ST depressions and T wave inversions in the left precordial leads and may be confirmed by biopsy of skeletal muscle and finding glycogen storage by Best s carmine stain

4 Rhabdomyoma (p 1070)

5 Interstitial (Isolated, Fiedler s) Myocarditis[400, 419]

These cases are characterized by very marked cardiac enlargement and by mild to severe interstitial infiltration of round cells lymphocytes, macrophages, plasma cells and sometimes eosinophils Degenerative myocardial changes are also observed Symptoms are likely to appear later in infancy than with other forms of congenital idiopathic hypertrophy There may be a history of a preceding or present infection or fever or neither of these Tachycardia is common and prominent There may be distress at feeding dyspnea and cyanosis Left and right sided congestive heart failure often develop abruptly with rapid progression often terminating in sudden death[244] There is clinical and roentgenologic evidence of gross uniform cardiac enlargement Gallop rhythm may be present and the liver is enlarged owing to congestive heart failure Respiratory distress

and pulmonary signs due to heart failure are often misinterpreted as pneumonia

Electrocardiographic changes usually consist of evidence of left sided heart strain flat T waves in all standard leads, occasional prolongation of the P R interval and low voltage of the QRS

Unlike the other forms of idiopathic hypertrophy and heart failure this disease may respond following therapy with digitalis and other measures against heart failure

Coronary artery lesions including necrosis of the media or medial hypertrophy and intimal fibrosis of the smaller coronary vessels may be found in cases of idiopathic cardiac hypertrophy

CONGENITAL VALVULAR DEFECTS

Congenital valvular defects are relatively common in association with one or more of the anomalies already discussed But except possibly for the bicuspid aortic valve they are rare as isolated lesions Pulmonic stenosis is the only one that is relatively common as an isolated lesion

PULMONIC STENOSIS (p 749)

PULMONIC INSUFFICIENCY (p 719)

AORTIC VALVULAR DISEASE

A *bicuspid aortic valve* alone or in combination with other lesions, such as coarctation of the aorta or subaortic stenosis is not infrequent It is uncertain how often the bicuspid aortic valve is of congenital and how often of rheumatic origin (p 864) Its chief significance is the frequency of a complicating bacterial endocarditis

Aortic valvular stenosis is usually stated to be rare but my personal clinical and pathologic observations suggest otherwise Grishman and his associates[190] reported 23 cases of congenital aortic or subaortic stenosis Marquis and Logan [11] also reviewed 23 cases of congenital aortic stenosis Campbell and Kauntze[6] presented evidence for the view that many cases of aortic stenosis in adults (aside from subaortic stenosis) are of congenital origin with superimposed degenerative and calcific changes rather than of primary calcific origin They stress the observation that in one half of 40 cases of aortic stenosis a murmur was heard in early childhood although a history of rheumatic fever was present in only two None of the patients presented evidence of mitral stenosis

Aortic stenosis is often due to a firm raised endocardial ring of fibrous tissue a few millimeters below the aortic valve (Fig 139) known as *subaortic stenosis* This appears to be analogous to infundibular stenosis in the right ventricle Subaortic stenosis may be associated with a second stenosis of the valve itself, so called double aortic stenosis A post stenotic dilatation of the aorta may occur similar to the post stenotic dilatation of the pulmonary artery in pulmonic stenosis Coarctation of the aorta narrowing of the aortic isthmus and bicuspid aortic valve are not infrequently associated [87] Subaortic stenosis probably represents an arrest of involution of the bulbus cordis [3] The left ventricle becomes hypertrophied

There are usually no symptoms or disability There may be distinct underdevelopment with severe stenosis (aortic dwarfs) There may be wide splitting of the first sound at the apex [333] There is a loud harsh systolic murmur and thrill maximal in the second right interspace or Erb s point and radiating to the cervical region (Fig 140) But the murmur may be heard lower over the sternal region or toward the apex There may be an associated diastolic murmur The second aortic sound in subaortic stenosis is usually normal and may even be accentuated[3 4] since the valve itself is intact

Roentgen ray examination reveals a large left ventricle and slight prominence of the ascending aorta due to post stenotic dilatation

Electrocardiography discloses left axis deviation and left ventricular hypertrophy

Pulse tracings over the cervical arteries show a characteristic slow initial rise an anacrotic notch systolic vibrations (carotid shudder) and a systolic plateau (Fig 140) Since the aortic valve itself is usually functioning normally the arterial tracing shows a sharp incisura due to aortic valve closure which is absent in cases of aortic valvular stenosis congenital or acquired [59]

In many cases the clinical course is asymptomatic but occasionally death has occurred relatively early because of a complicating bacterial endocarditis or congestive heart failure In cases involving the aortic valve itself angina pectoris syncope and heart failure are more likely to occur

The *diagnosis* is based on the history or finding of a harsh systolic murmur and thrill in childhood the absence of cyanosis and left axis deviation of the electrocardiogram The characteristic *carotid* pulse tracing is diagnostic According to Brofman and Feil,[59] subaortic stenosis is distinguished from aortic stenosis by the presence in the former of a sharp incisura accompanied by an aortic second sound of good quality

Treatment Six of 23 cases reviewed by Marquis and Logan [4] were submitted to aortic valvulotomy The valve was approached through the left ventricle and was ruptured by an expanding dilator without previous incision There were no deaths, but in two cases significant aortic insufficiency and cardiac enlargement were produced In the others there was a striking decrease in physical signs and a change in the form of the arterial pressure wave Electrocardiographic evidence of left ventricular hypertrophy in growing children with signs of aortic stenosis and especially attacks of syncope were regarded as indications for valvulotomy

Aortic atresia is rare The left ventricle is hypoplastic or nonfunctioning and oxygenated blood from the left atrium reaches the right atrium through a defect in the atrial septum Mixed venous and arterial blood passing from the right atrium to the right ventricle and pulmonary artery reaches the aorta by way of a patent ductus Intense cyanosis dyspnea great right sided cardiac enlargement and early death characterize the clinical picture

TRICUSPID VALVULAR DISEASE

Tricuspid stenosis with or without insufficiency is very rare [4]

Ebstein's disease[131, 134, 136, 643] is a congenital downward displacement of the tricuspid valve into the right ventricle Consequently the leaflets, instead of arising normally from the annulus fibrosus arise below this from the wall of the right ventricle The valve leaflets are usually deformed Occasionally the anterior leaflets arise normally from the ring There is no tricuspid regurgitation The portion of the right ventricle above the valve becomes incorporated into the right atrium (atrialized right ventricle) The right atrium is grossly enlarged Little blood thus flows into the right ventricle and pulmonary artery The right ventricle is diminished in volume The blood may reach the right ventricle through a sphincter like aperture in one of the deformed



Fig 139 *Subaortic stenosis male aged 67 Left ventricle opened to show aortic valve and subjacent ridge causing subvalvular stenosis*

valve leaflets There is an associated patency of the foramen ovale in the majority of cases, or there is an interatrial septal defect, but the septum may be intact in some cases A patent ductus may be present

Symptoms When there is an associated interatrial communication there is a right-to-left shunt through the opening and a distinctive clinical picture Dyspnea is a constant symptom There is usually marked cyanosis and slight clubbing The cyanosis is usually delayed but it may appear at birth, disappear and reappear with increasing severity after a few years Fatigability is common Squatting is unusual Occasionally there is no significant circulatory disturbance, no cyanosis[3, 18] and no symptoms due to the lesion as in the case of a woman who survived to the age of 79[5]

Examination reveals marked enlargement of the heart There is a diffuse systolic and often also a diastolic murmur over most of the precordium Gallop rhythm is usual The liver is large There are prominent "a and c waves in the jugular venous tracing

Fluoroscopic and roentgenographic examination disclose enlargement of the heart especially to the right (large right atrium) with a concave pulmonary artery salient small pulmonary arteries and clear lung fields

The electrocardiogram may show right bundle branch block and prolonged P R interval[408] The P waves are tall and may be of increased duration in leads II and III Paroxysmal ventricular premature beats are common

Angiocardiography discloses an enormous right atrium with persistent opacification due to long retention of the contrast substance There is poor visualization of the right ventricle and pulmonary artery The left side of the heart is visualized early by way of the interatrial communication

Catheterization The catheter may loop into the upper part of the right ventricle and meet an obstruction The right ventricular pressure is not elevated as in pulmonic stenosis with atrial septal defect from which Ebstein's anomaly must be distinguished

Diagnosis The diagnosis has been made during life[374, 210, 26, 37] The late onset of cyanosis absence of squatting distinctive cardiac enlargement and roentgenographic appearance of the heart and the systolic and diastolic murmurs can be diagnostic It may be mistaken for Fallot's tetralogy or for pulmonic stenosis with interatrial septal defect If the clinical features are not sufficiently distinctive angiocardiography and cardiac catheterization will differentiate them

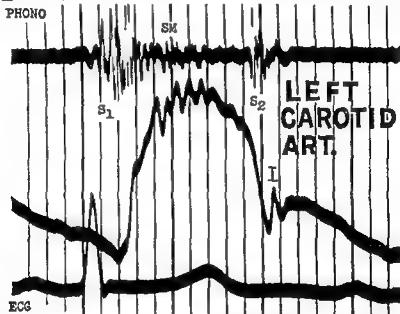


Fig 140 Subaortic stenosis Phonocardiogram and carotid artery tracing Prolonged high amplitude systolic murmur Anacrotic carotid pulse with systolic vibrations and plateau Sharp incisura (I) and normal second sound (S) indicate normal closure of aortic valve

Tricuspid atresia[12, 27, 87] results from faulty development, but its exact pathogenesis is uncertain Several varieties have been distinguished, but in all there is an atresia of the tricuspid valve, characterized by an imperforate atrioventricular canal, which is a simple membranous vault Therefore there is an interatrial communication to maintain the circulation There are two major forms of tricuspid atresia (1) *without transposition of the great vessels*, and (2), a less common form with a better prognosis, *with transposition of the great vessels*[13] Both forms are further subdivided into those with and those without pulmonic stenosis or atresia The group of tricuspid atresia without transposition but with pulmonic stenosis has a very high mortality during infancy but responds well to the Blalock ductus operation and therefore should be recognized early In the group without transposition a ventricular as well as atrial septal defect is present when the pulmonary artery is functioning but the ventricular septum is intact in cases with pulmonary atresia Dextrocardia and reversal of the aortic arch are often associated

In the cases without transposition of the great vessels the right ventricle is extremely small or rudimentary while the right atrium is greatly dilated The left ventricle is hypertrophied The pulmonary valve as well as the tricuspid may be atresic, since the right ventricle does not function

If the interatrial septal defect is small, the heart functions as a triloculate heart (pseudotriloculare-biatrium), blood passing from the right to the left atrium, thence to the left ventricle and aorta From the left ventricle some blood reaches the pulmonary artery and lungs by way of the ventricular septal defect If the ventricular septum is intact blood is supplied to the lungs from the aorta through a patent ductus arteriosus If the atrial septal defect is very large, both atria function as a single chamber and the heart as a biloculate chamber

When tricuspid atresia is associated with transposition of the great vessels, the aorta may arise from the right ventricle and be of small size, the patent pulmonary artery arising from the left ventricle The latter may also expel blood into the aorta through an interventricular septal defect Or the pulmonary artery, arising from the aorta, may be stenosed, and the aorta large and arising from the right ventricle The lung is then vascularized through an interventricular septal defect, patent ductus or bronchial arteries In general, there is little or no cyanosis in this group and a relatively favorable outlook

Clinical Features In the usual case, without transposition, cyanosis appears very early and death occurs in infancy Polycythemia and clubbing occur in those who survive long enough Attacks of syncope and exertional dyspnea are common There may be no murmur or a mesocardial systolic murmur which is heard all over the precordium In cases with a small atrial septal defect which offers resistance to the flow of blood from the right to the left atrium, blood is forced back to the inferior vena cava giving rise to a presystolic liver pulsation The cervical veins are prominent and show exaggerated pulsations

Roentgenology In the anteroposterior view examination reveals an enlarged globular heart with a sharp concavity in the region of the pulmonary conus which is rudimentary In the left anterior oblique view there is little or no shadow anteriorly where the right ventricle should be while the shadow of the left ventricle is enlarged There may be asynchronous pulsations of the anterior and posterior borders of the heart in this view, since the large right atrium replaces the right ventricle on the anterior border[272] The shadow of the great vessels is narrow and the pulmonic window is clear Clear lung fields are characteristic of tricuspid atresia without transposition of the great vessels but they may be obscured when there is an extensive bronchial collateral circulation in certain cases with transposition of the great vessel There may be a deficiency in the lower half of the right cardiac border (right ventricle) in posteroanterior and left anterior oblique views, which has been regarded as characteristic of tricuspid atresia But if the associated atrial septal defect is small relative to the size of the mitral orifice the right atrium may be so dilated and hypertrophied that the lower right cardiac contour is full not deficient[272]

Electrocardiogram The electrocardiogram reveals left axis deviation or the pattern of left ventricular hypertrophy The P waves may be enlarged due to atrial hypertrophy

Angiocardiography[135] discloses the dilated right atrium, interatrial communication (passage of contrast material from right to left

atrium) early filling of the aorta absence of the right ventricle and the position and chamber of origin of the great vessels

Cardiac Catheterization The catheter passes from the right atrium through the interatrial opening into the left atrium The pressure and oxygen concentration of right atrial blood are increased

The diagnosis of tricuspid atresia should be strongly suspected in a cyanotic patient with congenital heart disease if the left ventricle is enlarged and the electrocardiogram shows a left axis deviation or left ventricular hypertrophy

Treatment The cases of tricuspid atresia with rudimentary right ventricle and atrial septal defect as well as those of non functioning right ventricle with atrial septal defect pulmonary atresia and patent ductus are amenable to the Blalock Taussig (p 760) or Potts operation Essentially these are cases of tricuspid atresia without transposition of the great vessels but with pulmonic stenosis

Tricuspid insufficiency is a rare congenital lesion[24] It has been mentioned in association with ventricular septal defect (p 744) In the case described by Barrett and Urich[24] there were progressive cardiac enlargement small pulmonary artery shadows electrocardiographic evidence of right bundle branch block and atrial fibrillation a loud systolic murmur and thrill at the apex systolic pulsation of the cervical veins and liver, cyanosis, and eventual right heart failure

MITRAL VALVULAR DISEASE

Mitral stenosis is usually associated with an interatrial septal defect in so-called Lutembacher's syndrome (p 735) There is a difference of opinion as to whether the mitral lesion is of congenital or rheumatic origin but in my experience at least some cases are unequivocally congenital

A *congenital cleft of the mitral valve* with or without an atrial septal defect may produce the clinical picture of mitral regurgitation with left atrial and left ventricular enlargement systolic and diastolic apical murmurs and heart failure

Mitral atresia is associated with hypoplasia of the left cardiac chambers and aortic atresia and is combined with other defects such as complete absence of the interventricular septum (cor biatrium triloculare)[410] ventricular and atrial septal defects patent ductus arteriosus and with transposition of the great vessels Cyanosis may be absent or mild and intermittent until the onset of heart failure Roentgen ray examination discloses gross cardiac enlargement with enlargement of the right atrium and right ventricle and dilatation of the pulmonary arteries and superior vena cava[105]

ANOMALIES OF THE CORONARY ARTERIES

The most frequent coronary anomalies are the presence of more than two coronary ostia an unusual site of origin of some of the coronary arteries or an abnormal course The right coronary or the left coronary artery may be absent branches of the single coronary artery supplying all parts of the heart[330, 393, 394] In 3 of the 9 cases reported by Roberts and Loube[330] there was occlusion of the single coronary artery with ensuing myocardial infarction

Left Coronary from Pulmonary Artery Of grave clinical significance is the origin of the left coronary artery from the pulmonary artery, so that it carries venous blood to the heart[25] Necrosis and fibrosis of the left ventricle especially of the subendocardial region are consequences of the myocardial anoxia The small arteries or arterioles may be thrombosed Subendocardial fibroelastosis is usually present Marked dilatation of the heart is common and death usually occurs in infancy, though the patient occasionally reaches adult life if there are unusually good anastomoses between the branches of the left and right coronary arteries

Usually during the first month of life but occasionally later dyspnea and tachypnea prolonged time for feeding and diminished weight gain develop There then occur striking attacks of pain sweating and crying resembling angina pectoris with feeding or exertion Examination reveals tachycardia and rapid respirations but usually no murmurs or heart failure There is marked cardiac enlargement chiefly of the left ventricle The electrocardiogram usually shows changes indicative of anterior wall infarction The association of pain and distress on nursing cardiac enlargement without murmurs and the distinctive electrocardiographic changes should suggest the diagnosis Eidlow and

Mackenzie[133] made the correct diagnosis during life in a three months old infant on the basis of paroxysms of cardiac pain associated with sweating pallor cyanosis and dyspnea great enlargement of the heart, and inversion of T_1 and T_2 and deep Q_1 in the electrocardiogram In most of the cases in which the *right* coronary artery arises from the pulmonary artery there is no myocardial fibrosis cardiac enlargement or serious clinical consequences

Congenital arteriovenous fistula and aneurysm between the left circumflex artery and coronary sinus has been described[115] The clinical findings resembled those of a patent ductus arteriosus but the latter was excluded by cardiac catheterization, which showed that arterialized blood was entering the right atrium The patient died of congestive heart failure In a similar case simulating patent ductus arteriosus there was found at operation an anomalous left coronary artery communicating with the right ventricle[116]

PERICARDIAL DEFECTS

The parietal pericardium may be completely absent or only partially incomplete usually in the region of the pulmonary artery[117] In cases of ectopia cordis, the parietal pericardium may be missing or intact When the pericardium is missing, the fetus is usually non viable, when it is intact the outlook may be favorable The characteristic feature in the absence of the parietal pericardium is the complete mobility of the heart both on respiration and change of position of the body This may be demonstrable on physical and roentgenoscopic examination There may be no symptoms or thoracic pain circulatory disturbance and even death may result from kinking of the great vessels due to cardiac mobility An even more common complication in cases with partial or complete absence of the parietal pericardium is the frequency of pneumonia, pleurisy with effusion, empyema or pericarditis due to the juxtaposition of the heart and left lung without an intervening pericardial sac[154]

More rarely there is a diverticulum of the pericardium or failure of attachment of the parietal pericardium These are of no clinical significance unless the orifice of the diverticulum becomes occluded and the consequent distention of the diverticulum interferes with cardiac contraction

ANOMALOUS BANDS, CHORDAE AND PAPILLARY MUSCLES

Occasionally (2 to 3 per cent of hearts), there is a network of thread like strands or a fenestrated membrane in the right atrium continuous with the eustachian or thebesian valves[9] This is known as a Chiari network It may extend across the atrial cavity and be attached to the upper part of the interatrial septum It is believed to represent a residuum or persistence of the valvula venosa dextra together with the septum spurium It is usually an incidental postmortem finding, but it may be clinically significant in two ways First it may act as a favorable site for the formation of thrombi with consequent pulmonary embolism Second, it rarely gives rise to an unusual continuous or systolic murmur which may resemble a venous hum or be confused with the bruit de Roger

Anomalous chordae may extend across the left ventricular cavity from an individual papillary muscle to an attachment high up on a mitral cusp or to the left atrium They may cause confusing adventitious sounds or murmur Papillary muscles may have unusual sites or attachments, e g to a pulmonary valve

The left atrium may be subdivided into two chambers when the septum primum is deflected to the left leaving a cavity between it and the septum secundum Cardiac failure may supervene

CONGENITAL ARTERIOVENOUS ANEURYSM OR VARIX OF THE LUNG[118, 119] (CAVERNOUS HEMANGIOMA)

This condition is usually encountered among young adult males The lesion is usually single, but often there are multiple lesions Heredity may play a role, the anomaly has occurred in brothers[??] in a father and son[403] and in sisters[300] There may be a familial history of telangiectasia[??, 386] The clinical picture depends on the size of the shunt and there may be no abnormalities except roentgen ray findings with small shunts[121] With large shunts the lesion is characterized clinically by persistent cyanosis, polycythemia and clubbing of the fingers and toes by exertional dyspnea hemoptysis, chest pain,

dizziness syncopal or epileptiform seizures, Adams Stokes syndrome and occasionally by focal cerebral manifestations The clinical picture resembles and may be mistaken for that of cyanotic congenital heart disease or of advanced chronic pulmonary disease with cyanosis or polycythemia vera [414] The cyanosis is caused by the shunting of unoxygenated pulmonary artery blood into the pulmonary vein without passing through the pulmonary capillaries A continuous murmur may be heard over the site of the lesion

The heart does not usually become enlarged as in acquired arteriovenous fistula The cardiac output is essentially normal and there is no important change in circulatory dynamics in contrast with systemic arteriovenous fistulas [153] A bruit may be heard over the chest wall overlying the fistula Hemangiomata of the skin or mucous membranes are commonly associated Fluoroscopic and roentgenographic examination may disclose one or multiple nodular lobulated densities with branches into the pulmonary vascular markings [355 356] They are most common in the right lower lobe but occur frequently al o in the left lower lobe and less commonly in any other lobe The densities become larger during the Valsalva and smaller during the Muller experiment [6] They may or may not pulsate Hilar pulsations may be seen on the side of the aneurysms *Laminography* may distinctly how large vessels attached to a spherical lesion Angiocardiography is important in the differential diagnosis [381] Cure may be effected by resection of the aneurysms lobectomy or pneumonectomy [412] Bilateral resection of the involved pulmonary tissue for bilateral pulmonary arteriovenous fistulas has been reported [47]

DIAGNOSIS OF CONGENITAL HEART DISEASE

The diagnosis usually involves the recognition of the congenital nature of a cardiac lesion and the determination of the site and character of the lesion it elf The presence of an organic cardiac murmur of cardiac enlargement or of dyspnea or cyanosis and clubbing without bronchopulmonary disease or brain injury beginning in infancy or early childhood should suggest congenital heart disease Rheumatic heart disease is very uncommon before the age of five and rare before the age of three If the patient is first seen in late childhood or after puberty the congenital nature of the lesion may be suspected from the history of a cardiac murmur or other evidence of heart disease since birth or early childhood A harsh systolic murmur and thrill denote congenital heart disease if they are discovered before the age of 20 The absence of a history of rheumatic fever is confirmatory evidence

An analysis of the signs and symptoms usually permits a clinical diagnosis of the common forms of congenital heart disease Certain characteristic manifestations reveal the congenital origin of specific cardiac anomalies even when there is no history of a lesion since birth

Congestive heart failure occurring in an acyanotic infant should suggest patent ductus arteriosus coarctation of the aorta an ectopic tachycardia or one of the causes of so called idiopathic hypertrophy of the heart The occurrence of dyspnea on feeding associated with stridor suggests the possibility of a vascular ' ring especially a double or right aortic arch

Cyanosis and Cardiac Enlargement in Infancy and Later

Cardiac enlargement and cyanosis in infancy without an associated murmur suggest the diagnosis of complete transposition of the great vessels But cyanosis at or shortly after birth completely relieved by oxygen and diminished by crying suggests pulmonary atelectasis rather than congenital heart disease Methemoglobinemia from drinking well water rich in nitrates from wax crayons acetophenetidin acetanilid sulfonamides or dyes may simulate cyanosis But there are no cardiac enlargement no murmurs and no limitation of exercise Atresia of the aortic isthmus may produce a cyanosis which is limited to the lower extremities if there is no transposition while cyanosis is more intense in the upper half of the body if transposition and isthmus atresia are associated Tricuspid atresia and nonfunctioning right ventricle are distinguished by left axis deviation and left ventricular enlargement

If cardiac enlargement cyano is and a murmur are pre ent in infancy the diagnostic pos ibilities are very numerous and require systematic study of the location of the murmurs roentgenoscopy angiocardiography etc

After the first three years of life, cardiac enlargement murmur and cyanosis are usually due to tetralogy of Fallot, somewhat less commonly to pulmonary stenosis with interatrial septal defect, or the Eisenmenger complex and occasionally to transposed great vessels or tricuspid atresia, persistent truncus arteriosus, levocardia Taussig Bing heart and anomalous pulmonary venous drainage and others The cyanosis is usually less intense and starts later in childhood or only after puberty in cases of Eisenmenger complex or pulmonic stenosis with atrial septal defect as compared with that in tetralogy of Fallot

Murmurs

In early infancy there may be a generalized systolic murmur which only later assumes its characteristic quality and site of maximum intensity A rough loud murmur with maximum intensity in the second left interspace near the sternum may be due to a patent ductus arteriosus pulmonic stenosis or the tetralogy of Fallot Occasionally its maximum intensity is one interspace lower The murmur of a patent ductus arteriosus is usually a pathognomonic machinery like murmur extending through systole and diastole, but it may be absent in infancy or occur only during systole Then however there is usually electrocardiographic evidence of left axis deviation or hypertrophy When there is a patent ductus with reversal of flow, there may be only a systolic murmur or none but the distribution of cyanosis is diagnostic (p 770) The second pulmonic sound is accentuated In aortic septal defect the machinery murmur is heard maximally over the lower sternum or in the fourth left interspace

A venous hum gives a continuous murmur which however is loudest in diastole is heard also to the right of the sternum and changes in intensity with changes in position of the head and neck

A roaring systolic and sometimes diastolic murmur occurs in rupture of a congenital aneurysm of the sinus of Valsalva into the pulmonary artery or right chambers, but there is a history of sudden onset of the murmur in adult life

The murmur of pulmonary stenosis is purely systolic and the second pulmonic sound is often weak or absent A loud systolic murmur with maximum intensity in the third or fourth interspace to the left of the sternum, should suggest an interventricular septal defect The murmur becomes distinctly weaker toward the clavicle or apex but is often transmitted to the left scapular region The atrial septal defect is associated with a variable murmur which may also be located in the third left interspace near the sternum Systolic murmurs in the interscapular regions axilla or along the sternum may be found in cases of adult coarctation of the aorta with well developed collateral circulation A harsh systolic murmur and thrill loudest in the second right interspace, suggests subaortic or aortic stenosis An apical diastolic murmur may occur with an atrial septal defect, interventricular septal defect or a patent ductus arteriosus

In practice, the murmur and history suggest the presence of congenital heart disease, but, except in the case of a patent ductus arteriosus or aortic septal defect, the murmur is not characteristic of a specific lesion However, if one considers the murmur in connection with the absence or presence of cyanosis the possibilities are usually narrowed to (a) atrial or ventricular septal defect or isolated pulmonic stenosis in cases without cyanosis or (b) tetralogy of Fallot, Eisenmenger's syndrome, pulmonic stenosis with interatrial septal defect, patent ductus with pulmonary hypertension and reversed shunt, tricuspid atresia or cases of single ventricle or single outflow tract when there is cyanosis The individual conditions in each group can then be differentiated as a rule by the site of the murmur and the nature of the second pulmonic sound by the time of onset of cyanosis when present, but chiefly by the fluoroscopic and roentgenographic appearance, especially by increased or decreased vascularity of the lung fields

Thrills are not diagnostic They do help to confirm the organic nature of a systolic murmur Furthermore in acquired heart disease they occur, as a rule, in systole over the aorta (aortic stenosis) or in diastole over the apex (mitral stenosis) Thrills in the second, *third* or fourth left interspace near the sternum almost invariably indicate the presence of congenital heart disease, except when there *is a* sudden perforation or tear of a cardiac structure

Roentgenologic Signs

Roentgen ray examination of the chest *is* invaluable in the diagnosis of many of the common congenital cardiac lesions, but only a

few of these are associated with a pathognomonic cardiac contour With some lesions the roentgen ray configuration of the heart is either fairly characteristic or is of great diagnostic help when interpreted in association with the clinical history and physical signs Fluoroscopy oblique views and examination after a barium swallow are essential in addition to a conventional roentgenogram of the chest

The diagnosis of *dextrocardia* can be made from the roentgen ray examination alone The bulk of the cardiac shadow is to the right of the midline The right leaf of the diaphragm is lower than the left In cases of true dextrocardia the electrocardiogram will prove the diagnosis

Adult coarctation of the aorta is often associated with smooth notching of the lower borders of the posterior ribs and occasionally with a localized defect in the descending arch of the aorta when viewed in the left anterior oblique position and with other distinctive signs (p 777) Hypertension weak or absent femoral pulsation and evidence of collateral circulation in the chest wall are also present in most cases

Persistent *double aortic arch and right sided aortic arch* presents distinctive features a pulsating shadow of the right aortic arch to the right of the sternum small or absent left aortic knob displacement of trachea and especially of the barium filled esophagus to the left and forward

Anomalous entrance of the pulmonary veins into the right atrium superior vena cava etc *persistent left superior vena cava aberrant right subclavian artery* and *pulmonary arteriovenous fistula* all have distinctive roentgen ray appearances which have been described

Even in the absence of a distinctive abnormality the roentgenologic examination of the chest usually helps to differentiate the various lesions if attention is paid to (1) the presence of cardiac enlargement and the chamber involved (2) the prominence of the pulmonary artery and prominence and pulsation of the main hilar arteries (3) the caliber of the pulmonary vessels and consequent clarity or engorgement of the lung fields

Among the acyanotic lesions *atrial septal defect* is likely to be associated with enlargement of the heart involving the right atrium and ventricle but especially with a large pulmonary artery pulsating hilar vessels and engorged pulmonary vessels In contrast in *isolated pulmonic stenosis* there may be pulmonary artery enlargement due to post-stenotic dilatation but the peripheral vessels are diminished in caliber and the lung fields clear *Ventricular septal defect* may be associated with a normal sized heart pulmonary artery and branches But with a high (large) septal defect there may be a large pulmonary artery and vessels and differentiation from atrial septal defect depends on cardiac catheterization studies *Patent ductus and aortico pulmonic septal defect* may resemble interatrial septal defect but the murmur is pathognomonic there is a large pulse pressure and there is usually left axis deviation in the electrocardiogram *Persistent truncus arteriosus* is usually unaccompanied by cyanosis and can be distinguished by the prominent aortic knob enlargement of the heart especially the left ventricle and the absence (indentation) of the pulmonary artery salient

Among the lesions associated with cyanosis a diminished caliber of the pulmonary arteries with clear lung fields and usually an indentation of the pulmonary artery salient is observed in tetralogy of Fallot tricuspid atresia (without transposition) and Ebstein s anomaly In pulmonic stenosis with right to-left shunt through an atrial septal communication the pulmonary vessels are small but the main artery is prominent owing to post-stenotic dilatation In some cases of tetralogy of Fallot in which the pulmonic stenosis is valvular the appearance may be similar and differential diagnosis depends on catheterization and angiocardiographic studies Tricuspid atresia is distinguished by the frequent absence of the right ventricular shadow and by left ventricular hypertrophy in the electrocardiogram Ebstein s anomaly is differentiated by the very large right atrium and the usual right bundle branch block in the electrocardiogram

The other relatively common cyanotic cases are associated with *increased caliber* of the *pulmonary* vessels and include Eisenmenger s syndrome (or large ventricular septal defect with right-to-left shunt) transposition of the great vessels patent ductus or aortic septal defect with reversal of flow (marked pulmonary hypertension) and pulmonary atresia or single ventricle or single outflow tract (including pseudo-truncus arteriosus) in which the lungs are supplied by

enlarged bronchial arteries Eisenmenger s complex is distinguished in this group by late and mild cyanosis transposition of the great vessels by deep cyanosis from birth, rapid progressive cardiac enlargement and often a narrow vascular pedicle The conditions with large bronchial arteries are characterized by coarse stippling of the hilar vascular markings

Other abnormal cardiac silhouettes are not characteristic but aid in confirming a diagnosis made on other grounds or in suggesting the presence of cardiac disease Generalized cardiac enlargement without murmurs may be due to a bilocular or trilocular heart, origin of a coronary artery from the pulmonary artery glycogen storage disease of the heart or cases of so called idiopathic hypertrophy (p 784)

Electrocardiogram[404 107 431 373]

The electrocardiogram is characteristic in cases of true dextrocardia with situs inversus Distinctive electrocardiograms have been described in infants with idiopathic cardiac hypertrophy without murmurs due to anomalous origin of the left coronary artery from the pulmonary artery (p 791) and to glycogen disease of the heart (p 786) Otherwise the electrocardiogram does not generally afford specific diagnostic aid to individual congenital cardiac diseases But the presence of right or left or combined ventricular hypertrophy when considered with the presence or absence of cyanosis and the roentgenologic findings in the heart and lung fields, may aid considerably in the differential diagnosis

Left axis deviation and left ventricular hypertrophy in a noncyanotic infant with a systolic murmur would suggest patent ductus arteriosus, subaortic or aortic stenosis or coarctation of the aorta In older children the typical murmur in patent ductus and other findings in coarctation and aortic stenosis would be more diagnostic *Left ventricular* hypertrophy in a non cyanotic infant with cardiac enlargement and no murmur suggests idiopathic cardiac hypertrophy (fibroelastosis) Electrocardiographic evidence of left *ventricular hypertrophy in a cyanotic infant* with a cardiac murmur would suggest tricuspid atresia Left axis deviation is common in cases of Eisenmenger s complex with combined ventricular hypertrophy

Most of the common congenital cardiac lesions other than patent ductus arteriosus coarctation of the aorta aortic stenosis and tricuspid atresia, are associated with right ventricular hypertrophy Attempts have been made to correlate different distinctive patterns with individual diseases associated with right ventricular hypertrophy, based on differences in hemodynamic disturbance [70 127 ...] However, due regard must be maintained for electrocardiographic changes that occur with age, and for differences due to degree of right ventricular hypertrophy rather than to specific etiologic disease or hemodynamic disturbance But differences in patterns may be related to the site of ventricular hypertrophy, since hypertrophy does not occur uniformly throughout the right ventricle, e g, certain lesions such as pulmonic stenosis involve predominantly the outflow tract whereas others, such as interatrial septal defect, involve primarily the inflow tract Thus, incomplete right bundle branch block ("diastolic overloading"[70] or "surcharge" pattern of right ventricular hypertrophy) is characteristic of interatrial septal defect but also occurs commonly in Ebstein's disease and sometimes in ventricular septal defects and other congenital cardiac lesions The "systolic overloading" or "barrage" pattern of right ventricular hypertrophy is observed in cases of isolated pulmonic stenosis and is characterized by a tall R wave in V_1 and other right precordial leads, in association with S-T depressions and T wave inversions in these leads This pattern is rarely if ever seen in tetralogy of Fallot and helps to distinguish this complex from pulmonic stenosis with intact ventricular septum but with atrial septal defect On the other hand incomplete bundle branch block has been observed in 19 of a series of 50 cases of isolated pulmonic stenosis[365] Electrocardiographic evidence of combined ventricular hypertrophy is common in ventricular septal defects and in some cases of patent ductus arteriosus with moderate pulmonary hypertension and in the Eisenmenger and Taussig Bing complexes Right axis deviation in association with the characteristic machinery murmur of patent ductus *denotes an additional lesion* usually pulmonic stenosis or an interventricular septal defect as well

Angiocardiography[152 170] (p 11)

Angiocardiography has become one of the most valuable techniques in the diagnosis of congenital heart disease It reveals with more certainty than the conventional roentgeno-

gram the specific chambers or vessels affected by enlargement or malposition It discloses the sequence of the circulation It differentiates between aneurysms and thoracic tumors unrelated to the cardiovascular system When surgical correction of a cardiac anomaly is contemplated angiocardiography serves to confirm the preoperative diagnosis discloses or excludes associated anomalies and reveals the size position and configuration of structures important to the surgeon

The technique has been described (p 11) For more precise diagnosis selective angiocardiography may be employed (p 15)[34]

Angiocardiography permits a precise diagnosis of dextrocardia persistent left superior vena cava right aortic arch and coarctation of the aorta but retrograde aortography yields a more distinct picture in the latter Dextroposition of the aorta and right to-left shunts in the tetralogy of Fallot and Eisenmenger are usually clearly disclosed by premature visualization of the aorta and right ventricular enlargement in both diminutive pulmonary arteries in the former and normal or enlarged pulmonary arteries in the latter Similarly a right to left interatrial shunt is disclosed by premature opacification of the left atrium ventricle and aorta and the interatrial defect may be visualized A patent ductus may be indicated by persistent visualization of the pulmonary artery and occasionally by a dilatation of the aorta at the site of the ductus The course of the blood stream and the nature and position of the various chambers and great vessels are often disclosed by angiocardiography in conditions with transposition of the great vessels tricuspid atresia pulmonary atresia Ebstein's anomaly of the tricuspid valve and conditions with a single outflow tract

Retrograde Aortography (p 16)

This technique is often superior to intravenous angiocardiography in demonstrating or excluding lesions of the thoracic aorta or aortic arch especially in infants Retrograde aortography is particularly valuable for accurate delineation of the character and extent of the constriction in coarctation of the aorta and the concomitant presence of a patent ductus arteriosus or other associated lesions Retrograde aortography has been successfully employed to differentiate patent ductus arteriosus aortic septal defect coarctation of the aorta and truncus arteriosus from lesions such as a high interventricular septal defect and congenital aortic stenosis[105]

Hypertension in a young person should always suggest the possibility of adult coarctation of the aorta A blood pressure which is significantly less in the lower than in the upper extremities weakness or absence of the femoral pulse evidence of a collateral circulation in the chest wall and notching of the lower borders of the ribs observed roentgenoscopically prove the diagnosis The possibility of congenital heart disease should also be considered in cases of young persons with cerebrovascular accidents in subjects with congenital anomalies such as mongolism and in patients with subacute bacterial endocarditis

Circulation Time Studies

The presence of a venous arterial (right-to-left) shunt may be demonstrated by the administration of ether as in the tests for determining the circulation time (p 214) When such a shunt exists the ether reaches the systemic capillaries and causes distinct unpleasant paresthesias of the skin of the face and subsequently of the extremities[9] This has been observed particularly in cases of the tetralogy of Fallot but it probably also occurs occasionally in cases of atrial or ventricular septal defects or patent ductus arteriosus when the usual left-to right shunt is reversed It also occurs in trilocular or bilocular hearts or in cases with extensive septal defects which are practically tantamount to bilocular hearts in which there is a fairly free mixing of arterial and venous blood even when the major current is in one direction In children as little as 1 or 2 minims of ether may produce the effect (See also intracardiac Evans blue right ventricle-to-ear time p 759)

Cardiac Catheterization (see also p 74)

In cases of interatrial septal defect the right atrial blood oxygen content significantly exceeds (by 2 volumes per 100 cc or more) that of the superior vena cava or the average of both venae cavae The catheter may pass through the septal defect When the pulmonary veins empty into the right atrium the right atrial blood oxygen is high and when all the veins drain into it the oxygen content equals that of a peripheral artery

In cases of interventricular septal defect the right ventricular blood oxygen content significantly exceeds (by 1 vol per 100 cc or

more) that of the right atrium Similar findings are noted in cases of tetralogy of Fallot and Eisenmenger, but with tetralogy of Fallot the pulmonary arterial pressure is lower than that of the right ventricle The catheter may enter the septal defect or the overriding aorta

In cases of patent ductus arteriosus the pulmonary arterial oxygen exceeds that of the right ventricle by at least 0 5 volume per 100 cc The catheter may enter the ductus

In patent ductus with reversal of flow the right ventricular and pulmonary arterial systolic pressures are greatly increased and equal or exceed systemic blood pressure

In uncomplicated pulmonic stenosis the pulmonary artery pressure is low or normal, that of the right ventricle increased

Inhalation of Oxygen

A marked rise in arterial oxygen saturation on breathing oxygen suggests intrinsic pulmonary rather than congenital cardiac disease as the cause of cyanosis

Indicator Dilution Curves

Distinctive dilution curves have been observed following the rapid injection of 0 5 mg per kilogram body weight of the Evans blue dye T 1824 into an antecubital vein[300] or catheter The varying concentration of the dye in arterial blood is measured continuously at the ear by a double scale ear oximeter or at the radial artery by a cuvette oximeter for whole blood Dye curves associated with left to right shunts are similar and characterized by a relative reduction in peak concentration of the dye and a prolongation in the disappearance time of the curve [64] These abnormalities can be related quantitatively to the magnitude of the shunt, but do not disclose the site of the shunt Dye dilution curves have also been obtained in cases of anomalous entrance of the pulmonary veins into the right atrium[300] and various forms of cyanotic congenital heart disease [391 90]

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Chapter 31

RHEUMATIC FEVER

Etiology Pathogenesis and Pathology

GENERAL CONSIDERATIONS

In the following discussion rheumatic fever is used to denote the general disease and rheumatic heart disease its cardiac manifestations Cardiac disease is the most serious manifestation of rheumatic fever It is erroneous to consider cardiac involvement merely a complication of this disease, because it occurs almost as often as any other symptom The heart rarely escapes damage in the chronic life history of rheumatic fever Since there is no specific reliable test for this disease only a complete understanding of all the manifestations of rheumatic fever will lead to a thorough recognition of the presence of rheumatic heart disease Even when cardiac involvement is absent in the early stages the physician s diagnosis of rheumatic fever is a warning of potential cardiac disease, since the victim of rheumatic fever is a favored candidate for acute recurrences which may spare the heart at first but rarely later Of 100 consecutive cases of rheumatic fever seen by Coombs [25] predominantly in children 59 presented signs of carditis at their first visit and many of the others developed such signs later so that at least 75 per cent eventually manifested some cardiac lesion In a series of 1000 patients with rheumatic fever followed at least twenty years by Bland and Jones [7] about 800 developed cardiac disease *Practically the importance of rheumatic fever lies in the frequency and seriousness of its cardiac lesions*

Incidence and Importance of Rheumatic Fever and Rheumatic Heart Disease

A host of statistical surveys attest to the relative frequency and importance of rheumatic fever and its cardiac disturbances The data vary according to studies made in urban or rural communities temperate, subtropical or tropical regions seasons of the year among school children or general population civilians and military personnel as well as with differences in diagnostic criteria and acumen

Patients with rheumatic fever form 3 to 7 per cent of the total sick admitted to the large general hospitals of Europe and the United States [101] Accurate determinations of the incidence of rheumatic fever and heart disease are impossible since the disease is not generally reportable and its diagnosis is frequently indefinite In the Scandinavian countries where rheumatic fever is reportable the incidence is between 1 and 3 per thousand Estimates based on various statistical analyses indicate that there are about one million cases of rheumatic heart disease in the United States [101] Reports from the British Ministry of Health[48] indicate that there were 25 000 fatal cases of rheumatic heart disease annually in England and Wales that these formed 40 per cent of all cardiac deaths and that in two thirds of these cases heart disease developed between the ages of 5 and 15

The highest incidence of rheumatic fever and rheumatic heart disease is among children and adolescents According to studies in the schools of several large cities rheumatic heart disease was encountered in 2 to 4 per thousand children between the ages of 6 and 19 [62] In New England and in London the incidence is closer to 2 per cent Keith[71] estimated that rheumatic heart disease occurs in [illegible] [illegible] to 1 36 per cent of American 0 1 to 2 08 per cent of British and 0 36 to [illegible] 92 per cent of Canadian school children Maresh et al [85] found the incidence of rheumatic heart disease to be [illegible] to 7 per 1000 among sixth grade school children in Colorado The seriousness of rheumatic heart disease among young people is

indicated by mortality statistics In the age groups between 5 to 9, 10 to 14 and 15 to 19 rheumatic fever and heart disease rank first as the cause of death, exceeding such diseases as tuberculosis and appendicitis as well as the combined mortality from all of the common contagious diseases Between 20 and 24 rheumatic fever ranks second only to tuberculosis as a cause of death Recent statistics indicate that there has been a reduction in the mortality rate among young people aged 5 to 24 from rheumatic fever (1 6 per 100 000 in 1943) and from rheumatic heart disease (about [illegible] per 100,000 in 1943) [9-6, 46, 141] By 1952 the mortality in this age range was 1 4 from rheumatic fever and only 1 9 per 100 000 from rheumatic heart disease [139] The incidence of new cases of rheumatic fever in the United States appears to have diminished strikingly in the past ten years [148] This may be related to the widespread use of the sulfonamides and antibiotics in nasopharyngeal and tonsillar infections but the progressively downward trend in children's mortality from rheumatic fever and rheumatic heart disease had been strikingly apparent even before the introduction of these drugs

Studies of the incidence of rheumatic heart disease and rheumatic fever among selective service applicants drafted troops and military personnel also attest to the importance of this disease [86] Among the first two million American selectees between the ages of 21 to 36 in the second World War, about 100 000 were found to be unfit because of cardiovascular disease [114] Reexamination by expert cardiologists of these disqualified individuals disclosed that at least 50 per cent suffered from rheumatic valvular defects [11]

The incidence of rheumatic heart disease relative to other etiologic types of heart disease varies in different localities according to the relative frequency of rheumatic fever In large cities of temperate zones such as New York Boston and London rheumatic heart disease represents between 25 and 30 per cent of all cardiac ailments In these places it ranks below coronary (atherosclerotic) and hypertensive heart disease Below the age of 50 it is the commonest type of organic cardiac ailment However, in many southern regions of the United States and in other localities with a high incidence of syphilis rheumatic heart disease is said to follow coronary (atherosclerotic), hypertensive and syphilitic heart disease in that order

Public Health Aspects

The frequency and importance of rheumatic fever and heart disease among school children drafted troops, applicants for life insurance and industrial workers emphasize the need for a public health program With due allowance for statistical inadequacies the available data teach the tragic lesson that in contrast with other major forms of heart disease rheumatic heart disease maims its victim before adolescence, impairs his efficiency and earning power throughout adult life and usually destroys him in his prime Many analogies with tuberculosis including the chronicity of rheumatic fever, social and economic predisposing factors, evidence of infectious etiology, as well as the greater mortality from rheumatic heart disease among young subjects, suggest the need for a public health program and the hope that such a program with respect to rheumatic fever, as with tuberculosis, will yield gratifying accomplishments However it is important to stress that any contemplated public health program for rheumatic fever is handicapped by our ignorance of its exact cause, and by the lack of some exact diagnostic test or specific treatment However, the prophylactic and therapeutic use of antibiotics against the hemolytic streptococcus may prove to be an effective means of attack against rheumatic fever and its recurrences

The need for a public health program and suggestions for such a program have been repeatedly presented [71, 101, 116] London has developed a scheme for the treatment and supervision of juvenile rheumatism[4] making rheumatic fever a reportable disease and providing beds for the treatment of rheumatic fever patients at public expense Special hospital units devoted exclusively to rheumatic fever have been built Emphasis has been placed on the chronic, relapsing nature of the disease Similar programs have been initiated in individual states in this country and a more concerted national effort in this direction has begun since the end of the war The Children's Bureau of the Department of Labor, the Rheumatic Fever Council of the American Heart Association and the Helen Hay Whitney Foundation have been most active

It is important to have a central integrating agency which keeps a registry of rheu

matic fever patients and which coordinates the work of various interested public and private agencies Rheumatic fever should be a reportable disease Expert clinical and laboratory facilities should be made available for aid to the physician in the diagnosis treatment and follow up of patients Case-finding methods should be improved and used more widely especially in schools and among siblings of known rheumatic fever patients Nursing hospital and social service facilities need to be enhanced Hospital facilities should take cognizance of rheumatic fever as a chronic disease as well as of its acute and subacute manifestations Rehabilitation programs should be developed and vocational guidance should be made available to rheumatic patients after convalescence Cooperation of employers should be obtained to aid in the placement of rheumatic patients in industry Research facilities need to be fostered and augmented with respect to epidemiology etiology clinical and laboratory features Educational programs should be designed for physicians nurses welfare workers and the lay public

DEFINITION AND CRITERIA

Rheumatic fever is a chronic inflammatory disease generally punctuated by recurrent acute episodes Its exact cause is unknown The strongest evidence for specificity as presented by pathologists, is the Aschoff body a granulomatous lesion analogous to the tubercle of tuberculosis or the gumma of syphilis There are additional pathologic lesions in rheumatic fever whose structure and distribution are almost specific for the disease Certain clinical features (e g mitral stenosis) are likewise of an almost specific nature

There is no special diagnostic laboratory test for rheumatic fever Fairly rigid criteria are available for diagnosis post mortem especially when Aschoff bodies are present But as will be indicated in the section on Pathology the diagnosis can generally be made even in the absence of these bodies The clinical diagnosis is dependent on less rigid criteria and requires a general consideration of the presence of numerous often seemingly unrelated clinical features including chorea cutaneous lesions hemorrhagic and pleuropulmonary as well as cardiac and arthritic symptoms Some of these, like erythema annulare subcutaneous nodules chorea or mitral stenosis occurring in children or young individuals are practically pathognomonic of rheumatic heart disease (See also p 840)

ETIOLOGY AND PATHOGENESIS

INFECTIOUS NATURE OF RHEUMATIC FEVER

Belief in the infectious nature of rheumatic fever is based on (1) the outbreak of epidemics (2) its occurrence with or after infectious diseases (3) a purportedly high familial association (4) the similarity of its climatic distribution and seasonal occurrence to that of other well known infections and (5) various clinical pathologic bacteriologic and immunologic considerations (infra)

1 On the basis of numerous hospital statistics Newsholme[97] pointed out that in certain years the incidence of rheumatic fever reached epidemic proportions Various epidemics of the disease were observed in army navy and air force barracks[3, 44, 19, 30, 66] Grenet[59] reported an epidemic in a regiment located in a certain sector When this regiment was removed to a distant area additional cases broke out among them On the other hand a new regiment which occupied the original affected area was unaffected These observations tended to indicate that the disease was spread from man to man independent of environment Epidemics of rheumatic fever have also been reported in various schools and in connection with the establishment of hospitals or convalescent homes for rheumatic cardiacs

2 A remarkable feature noted in these and other reports was the occurrence of the epidemics following outbreaks of acute tonsillitis pharyngitis or other respiratory infections and after scarlet fever (p 808) Of course it is generally impossible to be certain that these rheumatic outbreaks are truly epidemics and not merely simultaneous reactivations of the rheumatic process in rheumatic individuals by incidental respiratory infections

3 A number of writers have noted a relatively high incidence of rheumatic fever occurring in more than one member of a family[69] Paul and Salinger's[103] observations on the spread of rheumatic fever through families could be interpreted to indicate the infectious nature of the disease, for both the

initiation of the disease and periods of recurrent activity occurred simultaneously in different members of a given family

4 Rheumatic fever like several other infectious diseases, occurs rarely or infrequently in subtropical or tropical regions and in the warm and dry seasons of the year (p 813) In this respect it particularly resembles the streptococcal infections Years in which the incidence of rheumatic fever is high are associated also with a high incidence of these infections

5 Clinically rheumatic fever resembles other infectious diseases in the occurrence of fever sweats leukocytosis, increased rate of sedimentation of erythrocytes, skin lesions inflammatory pulmonary complications, etc Pathologists generally have accepted an infectious etiology of rheumatic fever because of the analogy of the specific Aschoff body with the specific granuloma in other infectious diseases because of the exudative and productive inflammatory lesions and because of the contiguous spread of the disease in the involved organs The bacteriologic and immunologic evidence for the infectious nature of rheumatic fever is that which will be shortly presented favoring the specific etiology of various bacterial agents

SPECIFIC CAUSE

No specific microorganism has been established as the cause of rheumatic fever Most of the evidence concerning a causative agent has related to streptococci But several other organisms have been invoked as the specific cause including the tubercle bacillus spirochetes and filterable viruses The theories as to causation of rheumatic fever can be considered as (1) hemolytic streptococcal, (2) allergic or hypersensitivity theory (3) non streptococcal

I The Hemolytic Streptococcus and Rheumatic Fever

The etiologic importance of the hemolytic streptococcus is based on clinical epidemiologic bacteriologic and immunologic observations

Preceding Pharyngitis or Tonsillitis The occurrence of sore throat or tonsillitis just prior to an attack of rheumatic fever is a common clinical observation The frequency with which reported epidemics of rheumatic fever were preceded by epidemics of pharyngitis or tonsillitis, occurring one to three weeks earlier, has been mentioned Schlesinger[111] in England and Coburn[20] in this country disclosed that the preceding pharyngeal infections were almost exclusively due to the hemolytic streptococcus Family outbreaks of hemolytic streptococcal infections (Lancefield's type A) are followed in some members of the family by suppurative lesions such as otitis, in others by rheumatic fever[101] A community outbreak of a milk borne epidemic of streptococcus sore throat was followed two weeks later by many cases of rheumatic fever[84] Epidemics of pharyngitis and tonsillitis in crowded populations of boarding schools have similarly been followed by rheumatic fever[44] Among naval recruits, crowded together in various stations during the last war cases of rheumatic fever appeared within a few weeks after hemolytic streptococcal infections hit their peak[44]

Preceding Scarlet Fever The association of rheumatic fever with scarlet fever was particularly noted by Cheadle[18] and others Since scarlet fever is due to an erythrogenic strain of hemolytic streptococcus and since typical clinical features[143] and pathologic evidence[41] of rheumatic fever and rheumatic heart disease are not infrequently observed one to three weeks after scarlet fever, this association may be interpreted to support the etiologic relationship of hemolytic streptococci to rheumatic fever

Hemolytic Streptococcus Infection Before Rheumatic Recurrences Recurrences of rheumatic fever and carditis commonly appear a few weeks after a hemolytic streptococcal pharyngeal infection In most of the reported epidemics of rheumatic fever, not only the initial attacks but also recrudescences followed infections with streptococcus *A* In a high percentage of cases of rheumatic fever among naval recruits in the last war a careful history and examination disclosed that the patient had previously experienced rheumatic fever and that the present attack represented a recrudescence following a hemolytic streptococcal infection Among carefully studied small rheumatic populations in rheumatic cardiac convalescent homes recurrences of rheumatic fever almost never appear except after a hemolytic streptococcal infection

These observations do not signify that all cases of tonsillitis scarlet fever or other hemolytic streptococcal infections are followed by an attack of rheumatic fever, even

if the patient has already suffered a previous attack. Such streptococcal infections in normal children, adolescents or young adults are probably followed by rheumatic fever in [illegible] per cent of cases. Among subjects with previous rheumatic fever a recurrence may be activated by streptococcus A infection in as many as 25 per cent or more. However many of the forty or more strains composing Group A hemolytic streptococci may differ fundamentally in virulence and particularly in their ability to precipitate or activate rheumatic fever. Thus in the same group of rheumatic children one epidemic of streptococcus A infection induced a recurrence of rheumatic fever in 50 per cent of the children, whereas two subsequent streptococcus A epidemic infections caused very few or no cases.[76] In some instances in which attacks of rheumatic fever are not preceded by overt respiratory infections, careful clinical observation may disclose mild pharyngitis or tonsillitis while nasal and pharyngeal cultures disclose the presence of hemolytic streptococci.

Similar Incidence of Streptococcus Hemolytic Infections and Rheumatic Fever. Hemolytic streptococcal infections and rheumatic fever are similar in their geographic, climatic and seasonal incidence. Seegal et al.[1] pointed out that scarlet fever, like rheumatic fever, becomes less frequent as one travels from northern to southern United States and that hemolytic streptococci are found in throat flora less commonly in the subtropical and tropical islands of the West Indies than in the northern half of the United States. Farquhar and Paul[38] noted a similarity in the seasonal incidence of hospital admissions in New Haven between that of rheumatic fever and that of scarlet fever, acute tonsillitis and erysipelas. Coburn[17] noted that patients with active rheumatic fever in New York had hemolytic streptococci in their throats. When the patients were removed to Puerto Rico, the hemolytic streptococci disappeared from their throats and the disease became inactive.

Streptococcus Hemolyticus Antibodies.[85] *Antistreptolysin.*[147, 208] Todd[131] reported the presence of an antigen termed *streptolysin* or *streptohemolysin* in the broth of hemolytic streptococcus cultures, which is hemolytic for the erythrocytes of rabbits. Two varieties have been described: streptolysin O (oxygen labile) and streptolysin S (oxygen stable).[62] The sera from horses which had been immunized with Streptococcus hemolyticus and the sera of humans convalescing from Streptococcus hemolyticus respiratory infections, including scarlet fever, were found to contain an antibody termed *antistreptolysin* (or antihemostreptolysin) which neutralized streptohemolysin and prevented its hemolytic action. It has also been found that about 70 to 90 per cent of patients suffering from acute rheumatic fever have abnormal quantities of antistreptolysin O in their serum.[130, 22] The finding has been interpreted to indicate a [illegible] relation between hemolytic streptococc[illegible] infections and rheumatic fever. The [illegible] ment of non suppurative complic[illegible], especially rheumatic fever, has been [illegible] excessive antibody formation of [illegible] elevated antistreptolysin found in the [illegible] globulin fraction is one example. T[illegible] of antistreptolysin in some cases of [illegible] streptococcal infection or of rhe[illegible] may be due to the failure of [illegible] streptococcal A strains to el[illegible] tolysin O.

The titer of antistrepto[illegible] significantly in the secon[illegible] set of the hemolytic strep[illegible] or tonsillitis, and reaches [illegible] the fourth to sixth week [illegible] minishes.[113] The titer is e[illegible] the highest dilution of [illegible] pletely inhibits the lysis [illegible] blood cells by one unit [illegible] Streptolysin O is now av[illegible] (Difco Laborato[illegible] inhibiting diluti[illegible] to contain 300 u[illegible] normal antistre[illegible] units, the seru[illegible] rheumatic feve[illegible] 250 to 1000 uni[illegible]

Antifibrinolysi[illegible] molytic streptoc[illegible] clot of human p[illegible] tion by these b[illegible] (plasminogen) [illegible] (or streptokina[illegible] vates plasmino[illegible] proteinase whi[illegible] the serum of p[illegible] streptococcal [illegible] with rheumati[illegible] amounts of [illegible] which neutra[illegible] it [illegible]

that patients with rheumatic fever have recently suffered from a hemolytic streptococcal infection

Hyaluronidase and 'Antihyaluronidase' (Hyaluronidase Inhibitor) The collagenous ground substance which is primarily affected in rheumatic fever contains hyaluronic acid as a principal substrate Many strains of hemolytic streptococci have been found to produce hyaluronidase, an enzyme capable of hydrolyzing hyaluronic acid and decreasing its viscosity, thereby favoring the passage of pathogenic microorganisms into collagen tissue Thus Guerra[58] demonstrated that a suitable dye when injected intradermally with hyaluronidase spread to a much greater extent than when the dye was injected with saline In patients with rheumatic fever, there was much more diffusion of the dye than in normal controls Hyaluronidase was interpreted as a 'spreading factor" produced by hemolytic streptococci and accounting for its invasiveness of collagen tissue in rheumatic fever Salicylates were found to inhibit this spreading effect [illegible] but these findings were not confirmed [60]

It is of interest that types 4 and 22 of the streptococcus A are the ones which produce large amounts of hyaluronidase but do not cause rheumatic fever The hyaluronidase effect appears to be antagonized by adrenocorticotrophic hormone The antistreptococcal hyaluronidase "antibody" or hyaluronidase inhibitor titer was found to be elevated in the sera of patients with rheumatic fever or other diseases which have been related to the hemolytic streptococcus [illegible] There is uncertainty whether antihyaluronidase is actually an antibody, hence some prefer to use the term hyaluronidase inhibitor The latter has been found to contain heparin

A mucin clot prevention test has been based on the ability of hyaluronidase to destroy the capacity of protein hyaluronic acid complex to form a typical mucin clot on addition of acetic acid Human serum contains a substance (hyaluronidase inhibitor) which inhibits the action of hyaluronidase on mucin clot prevention The mean titer of hyaluronidase inhibitor in the sera of patients with early active rheumatic fever was found to be higher than that of sera from patients with subsiding or inactive rheumatic fever, hemolytic streptococcal disease or non streptococcal infectious diseases [61]

Although the incidence of elevated serum hyaluronidase inhibitor and elevated antifibrinolysin and antistreptolysin titers is equally high in patients with rheumatic fever, there are many individual patients in whom only one or the other is elevated [106, 83] Stollerman et al [illegible] found a high initial titer of either antistreptolysin O antistreptokinase or antihyaluronidase in the sera of 95 per cent of patients who could be studied within the first two months of onset of an attack of rheumatic fever

Bacteriostatic Antibodies Streptococcus A type-specific bacteriostatic antibodies have been found to develop in the blood of patients following group A streptococcal infections [77] The presence of these antibodies is demonstrated by the phagocytosis of virulent strains of A streptococcus which produce large amounts of type specific M (protein) antigen Similar bacteriostatic antibodies have been demonstrated in the blood of patients with acute rheumatic fever [illegible]

Concomitant with the rise in individual antibodies in cases of rheumatic fever there is an increase in serum gamma globulin fibrinogen alpha globulins, mucopolysaccharides and mucoprotein

The *C reactive protein* is not specifically related to rheumatic fever or streptococcus A infections, and is discussed on page 836

Sulfonamide and Penicillin Prophylaxis and Treatment of Hemolytic Streptococcal Infections The incidence of rheumatic fever has been diminished significantly by active treatment of hemolytic streptococcal infections or by prophylactic use of sulfonamides[78] or penicillin[14] [illegible] to prevent such infections Rapid control of epidemics of hemolytic streptococcal infection in military barracks by chemotherapy or antibiotics was followed by a sharp diminution in new cases of rheumatic fever [illegible] These observations on the prophylaxis and treatment of hemolytic streptococcal infections add support for the theory of a causal relationship between such infections and rheumatic fever

Critique of the Hemolytic Streptococcal Theory In brief, the hemolytic streptococcal theory maintains that rheumatic fever is a phase in the life history of pharyngeal infection with streptococci of Group A *Phase I* is the primary hemolytic streptococcal infection Phase II is a subsequent quiescent period of one to three weeks during which a series of

events occur involving the action of streptococcal products and the complex reaction of the host to the streptococcus and its products (antigen antibody mechanisms) Phase III is the period of the active rheumatic inflammation and phase IV an inactive rheumatic stage which may become activated again by a hemolytic streptococcus infection Variations in the strain type and virulence of the infecting streptococcus and differences in susceptibility of the host account for the failure of many hemolytic streptococcal infections to be followed by active rheumatic disease Furthermore the continued presence of the hemolytic streptococcus or multiple hemolytic streptococcal infections may be necessary

It appears improbable that the hemolytic streptococcus per se is the causative organism directly responsible for rheumatic fever

(1) Blood cultures during active rheumatic fever are almost always negative Hemolytic streptococci have not been isolated with any regularity from rheumatic tissues

(2) Rheumatic fever or rheumatic heart disease has never been reproduced convincingly by hemolytic streptococci or indeed by any other means The spontaneous occurrence in rabbits and guinea pigs of myocardial inflammatory foci resembling Aschoff bodies is a source of misinterpretation of experimental results in these animals Neither could the claims of the experimental production of rheumatic fever in guinea pigs by the combination of vitamin C deficiency and the injection of hemolytic streptococci be accepted or substantiated[1 0] Kellner and Robertson[73] injected intravenously into experimental animals a proteolytic enzyme streptococcal proteinase obtained from hemolytic streptococci and produced selective necrosis of heart muscle However the lesions do not resemble those of rheumatic fever and no Aschoff bodies were produced

(3) The above mentioned findings of hemolytic streptococci in throat cultures in relation to subsequent attacks of rheumatic fever and the findings of hemolytic streptococcal antibodies have been contraindicated especially by Wilson and her associates[146] The frequent disappearance of hemolytic streptococci from the throats of rheumatic patients during the quiescent interval (phase II) and during rheumatic activity (III) is another objection leveled at the hemolytic streptococcal theory

The purported absence of throat infections prior to some attacks of rheumatic fever and the frequent failure of rheumatic subjects to suffer a recurrence despite a streptococcal throat infection are additional criticisms of the theory

However the seeming occurrence of rheumatic fever without previous throat infection and the isolation of group A streptococcus in only 50 to 60 per cent of patients during the acute phase of rheumatic fever[55] might be controverted if bacteriologic studies could be made with more regularity and by special bacteriologic techniques Moreover the frequent absence of rheumatic activity after a hemolytic streptococcal infection and the occasional absence of significant levels of antistreptolysins during rheumatic activity may be dependent on the particular type of hemolytic streptococcus responsible for the throat infection or special susceptibility of the host However there is still uncertainty as to whether rheumatic fever follows only specific types or strains of streptococcus A pharyngitis[107] At present the weight of evidence strongly supports the hypothesis that the hemolytic streptococcus (Group A) or specific types of this streptococcus are important in initiating or precipitating the first or subsequent attacks of rheumatic fever in susceptible individuals However the mechanism by which the hemolytic streptococcus actually produces the pathologic and clinical manifestations of the disease and the manner in which rheumatic fever activity persists for many months in the absence of demonstrable streptococci are among the important gaps in the streptococcal theory of rheumatic fever

2 Hypersensitivity Theory of Rheumatic Fever

The hypersensitivity or allergic theory has been proposed to account for some of the gaps in the streptococcal theory and for the failure to isolate a specific causative organism from the blood joint effusions or the affected tissues in cases of acute rheumatic fever and rheumatic heart disease

Theory of Hypersensitivity to Streptococcus A (Hemolyticus) At the present time the most widely accepted theory of the pathogenesis of rheumatic fever proposes that this disease results from infection with the hemolytic streptococcus but only in those subjects who exhibit an exaggerated immunologic response (hypersensitivity) to that organism or its

products[129] The evidence for the role of the hemolytic streptococcus has been presented The evidence for hypersensitivity to this organism is less direct

The general idea that rheumatic fever might represent some type of immunologic reaction was suggested by the analogy to serum sickness in which a latent period of 10 to 21 days elapses between foreign serum injection (sensitization) and the serum sickness reaction In rheumatic fever there is a similar interval between the hemolytic streptococcal pharyngitis and the subsequent appearance of active rheumatic fever[118] Furthermore, this interval appears to correspond to the interval required for the development of large quantities of circulating antibodies In both diseases fever non suppurative arthritis and cutaneous lesions are characteristic manifestations This concept appeared to be supported by a variety of studies in which lesions resembling those of rheumatic fever were induced in rabbits following the repeated injection of horse serum[74, [illegible], 110] However, discordant observations[18] have been made by others and despite some resemblance of the experimental lesions to those of rheumatic fever the latter disease as it occurs in humans has not been produced experimentally The belief that periarteritis is an allergic disease, the association in some patients of rheumatic fever and periarteritis nodosa,[41] and the claim that both periarteritis nodosa and rheumatic fever may be produced experimentally by the same technique of foreign protein sensitization[110] are also cited in support of the hypersensitivity theory of rheumatic fever But there are many differences between rheumatic fever and periarteritis nodosa[82]

That rheumatic fever is a hypersensitivity response to the hemolytic streptococcus is indicated by the exceptionally high concentration of antistreptolysin and other antibodies to hemolytic streptococcal antigens in patients with active rheumatic fever,[21, 61] as compared with subjects who do not develop rheumatic fever after hemolytic streptococcus pharyngitis However there are exceptions to this general observation Furthermore there is no universal relationship between the development of such streptococcal antibodies and rheumatic fever, thus high antistreptolysin O titers may be observed in only 70 to 90 per cent of cases of active rheumatic fever

Another example of the possible relationship of rheumatic fever to circulating streptococcal A antibodies is the observation that when penicillin is administered early in the course of a hemolytic streptococcal infection it both suppresses the development of antibodies and prevents rheumatic fever But Catanzaro et al,[11] by withholding penicillin until the ninth day after the onset of a streptococcus A infection, were able to prevent rheumatic fever without suppressing the antistreptolysin response These observations were interpreted to suggest that the development of rheumatic fever requires the presence of *living streptococci* throughout convalescence that some antigenic product of the streptococcus is produced continuously during the acute and convalescent phase and that rheumatic fever is the pathologic result of a hypersensitivity of the tuberculin or "delayed" type

In evaluating studies concerning streptococcal A antigens and antibodies it should be borne in mind that streptolysin antistreptolysin represents only one of a host of possible antigen antibody combinations and that the particular antigen antibody complex which may be responsible for rheumatic fever is as yet unknown Neither is it clear how the hypothesized antigen antibody reaction causes tissue damage or how its localization to specific tissues is determined It is also well to mention that there is no significant evidence relating the specific clinical manifestation of rheumatic fever with individual antibodies or their antigens

Autoantibody Theory Still another variant proposes that rheumatic fever is caused by autoantibodies[13] in response to damaged tissue of the host, and such antibodies result in further tissue damage and antigen formation Cavelti[12] produced antibodies to the heart and connective tissue as well as kidney of rats and rabbits, by repeated injections of emulsions of the homologous tissues in conjunction with killed streptococci On the basis of his experimental observations and the finding of autoantibodies to human heart in the blood of 75 per cent of patients with acute rheumatic fever Cavelti suggested the following hypothesis of rheumatic fever Streptococcal substances in combination with connective tissue, including that of the heart, produced an autogenous antigen (streptococcus heart) which incited the development

of specific antibodies The latter were thought to precipitate the rheumatic lesion by reacting with the streptococcal tissue antigen The observations of Cavelti have not been confirmed [37]

Shwartzman Reaction as a Possible Mechanism in Rheumatic Fever Another suggested mechanism by which the hemolytic streptococcus host relationship may precipitate rheumatic fever involves the generalized Shwartzman reaction Cardiac tissue necrosis with giant cells and other inflammatory cells fibrinoid change in the coronary arteries pericarditis and mild valvulitis were induced when animals were prepared by injection of hemolytic streptococci and the lesions induced by subsequent injection of endotoxins from gram negative bacteria [123] [131] Furthermore leukocyte platelet thrombosis of capillaries and small veins similar to the lesions occurring in the Arthus and Shwartzman phenomena were found in the hearts of patients dying in the course of rheumatic fever [1 2]

Whereas Group A streptococci are unable to cause rheumatic fever directly it is possible that repeated streptococcal infections by their effect on the host create new substances which are then capable of producing rheumatic fever Thus although cell free streptococcal culture filtrates or heated streptococci are inactive in the preparation of rabbits for the generalized Shwartzman reaction soluble extracts of rabbit s skin which has been subjected to multiple infection by hemolytic streptococci are effective in preparing rabbits for this reaction [121] Furthermore cardiac lesions closely resembling those of rheumatic fever were induced in rabbits following repeated skin infections with Group A streptococci [91] These studies on the concept of the hemolytic streptococcus host combination have at present only an indirect speculative bearing on the pathogenesis of rheumatic fever Rheumatic heart disease as seen in the human has not been produced in animals on the basis of this or other concepts

3 Non streptococcal Theories of Rheumatic Fever

Besides the streptococci, a variety of organisms have at times been implicated as the specific causative agent of rheumatic fever In particular the failure to isolate with regularity a specific bacterial agent has suggested that the responsible cause may be an unidentified virus Schlesinger Signy and Amies[119] observed particles resembling virus elementary bodies obtained by high speed centrifugation of pericardial or pleural fluid from persons with acute rheumatic pericarditis Saline suspensions of these bodies were agglutinated by sera of patients with active rheumatic fever Virus bodies were observed by Coles[24] in Giemsa stained spreads of pericardial fluid from cases of acute rheumatic fever but similar bodies were seen in the pericardial fluid of 25 of 50 nonrheumatic cases Eagles and Bradley[29] also demonstrated the nonspecific character of these agglutination reactions

Claims for the tubercle bacilli[81] and for pleuropneumonia organisms have not been substantiated [117]

PREDISPOSING CAUSES OF RHEUMATIC FEVER

Geography and Climate

It has long been recognized that rheumatic fever is essentially a disease of temperate climates and is relatively rare in the tropics The disease is common in Great Britain and France but rare in the tropical possessions of these nations [3] In Canada and the United States the incidence of rheumatic fever diminishes progressively as one proceeds southward [4] Paul and Dixon[107] found the incidence of rheumatic heart disease ten times as frequent in a group of Indian school children living close to the Canadian border (Wyoming and Montana) as among a similar group near the Mexican border (Arizona) An analysis of numerous Army Air Force posts in the United States in the last World War revealed a very high incidence of rheumatic fever in the northern Rocky Mountain regions and Great Lakes as compared to those near the Mexican border and Gulf of Mexico [64] Coburn[19] *emphasized the* rarity of rheumatic fever in Puerto Rico and noted the subsidence of symptoms and absence of recurrences in rheumatic patients transported there from New York On the other hand I have frequently observed active rheumatic fever in Puerto Ricans who have come to live in New York City

The significance of a possible relationship between geography and climate and the incidence of rheumatic fever must be evaluated with caution In the first place there is much less certainty than formerly as to the relative rarity of rheumatic fever and heart disease in southern and tropical countries Chavez[16] reported a surprisingly high inci

dence of rheumatic heart disease in Mexico, and other observers have discovered rheumatic fever or heart disease in subtropical or tropical places in which the disease was considered almost non existent, such as Ceylon India China Costa Rica Hawaii and Panama In the second place, admitting differences in incidence depending on geography and climate it is uncertain whether such correlation depends on meteorologic conditions (temperature rainfall, barometric pressure etc), racial differences economic and dietary differences bacteriologic flora and immunity, or especially crowding with its predisposition to the spread of infection

Season

The greatest incidence of rheumatic fever is in the colder and wetter months of the year, and most commonly in January February, March and April [101] In Great Britain a high incidence has been reported as beginning somewhat earlier, e g , October or November and continuing through the spring [45] In India Kutumbiah[79] observed no seasonal variation in the occurrence of rheumatic fever The seasonal relation to streptococcal or other respiratory infections has been repeatedly noted and this may account for the seasonal incidence of rheumatic fever [107] The seasonal incidence is probably not related to cold or dampness as such for in World War I rheumatic fever occurred much less commonly among troops in action in cold damp trenches than among those in warmer and drier but overcrowded barracks

Urbanization

Rheumatic fever occurs much more frequently in industrialized, well populated cities than in rural areas [6] The correlation is not linear for the mortality rate from rheumatic heart disease is higher in Denver, Colorado than in many much more populous and industrialized cities To the extent that urbanization predisposes to rheumatic fever, it appears that crowding and the consequent spread of infection are the important factors

Economic Status and Housing The Factor of Crowding

British investigators have emphasized the greater frequency of rheumatic fever among the lower economic groups [2 4 45 4 67] In one series there was an incidence of 13 1 per cent rheumatic patients in the outpatient department and only 0 7 per cent in private practice Nevertheless there is some evidence that rheumatic fever, unlike tuberculosis, does not strike the very destitute but rather those above this level In this country poverty has not appeared to be a significant predisposing factor

The question of housing is closely related to economic status Rheumatic fever has often been associated with dampness in general and damp housing in particular Geographic studies of the incidence of rheumatic fever in London show a close correlation with proximity to the course of old streams [13] In New York, Ingermann and Wilson[69] found the smallest percentage of cases in districts farthest from the river fronts A high incidence of rheumatic fever has been reported in houses judged to be damp by British sanitation inspectors[137] and particularly among individuals residing in basements or ground floors without cellars beneath them Other reports minimize the importance of dampness in housing [81]

It is probable that economic status and housing are predisposing factors in rheumatic fever, chiefly in so far as they lead to crowded living conditions An analysis of rheumatic heart disease in Bristol England, revealed that its incidence was closely related to crowding in the home [105] The factor of crowding and consequent predisposition to the spread of hemolytic streptococcal infection was also considered significant in explaining the greater frequency of rheumatic fever in northern as compared with southern United States,[102] and in accounting for the occurrence of epidemics in boarding schools, hospital wards and barracks [144]

Family Incidence, Heredity and Constitution

A number of investigators have called attention to a significantly high family incidence of rheumatic fever [15 69 103] Cohn[2] stated that 8 to 10 per cent of members of rheumatic families experienced rheumatic fever but only 2 9 per cent of the families of nonrheumatic controls Similar observations have been made by Massell and Jones[85] and others A significant familial tendency to rheumatic fever is however, by no means universally accepted as fact In my own experience dealing chiefly with inactive rheumatic heart disease it is very exceptional to encounter more than one member of a family with rheumatic mitral stenosis or rheumatic aortic insufficiency It should be pointed out that the diagnosis of mitral stenosis or aortic insuf

ficiency is subject to less inaccuracy than the diagnosis of rheumatic fever

A high family incidence has been variously attributed to infectious communicability of rheumatic fever to similar environmental factors in members of the same family to hereditary or constitutional susceptibility or to a combination of these Evidence for frequency of rheumatic fever among certain anthropologic types or in individuals with certain pigmentation of skin eyes hair (e g, red hair) is unconvincing Wilson and her associates,[145] after many years of careful observation of families with rheumatic fever have concluded that the susceptibility to this disease is an inheritable characteristic, dependent on a single autosomal recessive gene

Age

About 90 per cent of first attacks of rheumatic fever occur between the ages of 5 and 15 More occur between 5 and 10 than between 10 and 15 Less frequently rheumatic fever begins between the ages of 15 and 20 between 1 and 5 or between 20 and 25 or older, in the given order[6] Reports of clinically active rheumatic fever in old individuals[51] are diagnostically unconvincing Thus in its primary stages rheumatic fever is essentially a disease of elementary school children The probability of a first attack and the tendency to recurrence diminish significantly after puberty is established Rheumatic fever among military personnel in the last war occurred chiefly in the youngest recruits, in many of these a careful clinical history and examination usually disclosed a previous attack As a rule, an upper respiratory infection precedes the episode of acute rheumatic fever by two weeks in the young adult as it does in the child[65] The age incidence of rheumatic fever has been related to the incidence of Group A beta hemolytic streptococci in the throat at various age levels[1 6] In young children (ages 6 to 9) Group A organisms were recovered from throat cultures twice as frequently as in older children (ages 12 to 15) and six times as frequently as in adults

Rheumatic fever is very uncommon in the first two or three years of life In infancy it is extremely rare Denenholz and Rambar[8] reported a case in a 10 day old infant Most of the reported cases in infancy are instances of placental infection from rheumatic mothers or infection in the sucklings of such infected mothers The youngest case I have seen concerned a seventeen months old child who, two days after a fall suffered pain in an ankle associated with fever and pulmonary symptoms Postmortem examination shortly afterward revealed myocardial Aschoff bodies and other evidence of active rheumatic heart disease

Sex

There is a slightly greater incidence among females chiefly because of the preponderance of females affected by chorea[3 101] Excluding the latter the incidence is essentially the same in both sexes

Race

The data are inconsistent regarding racial differences in the incidence of rheumatic fever Some statistics appear to indicate a greater frequency of the disease among the Irish the Anglo Saxons and the Jewish races The incidence among Negroes has been found to be higher equal to or lower than that among white subjects in different locations At present, there is a generally prevailing higher mortality among non white than among white children most probably due to adverse socio-economic environment rather than to constitutional differences in susceptibility

Nutrition Endocrine Factors

Undernutrition and improper nutrition have been considered as factors predisposing to rheumatic fever Epidemiologic and experimental evidence that a deficiency of ascorbic acid may be an etiologic factor was presented by Rinehart Connor and Mettier[111] The diet of patients with rheumatic fever has been reported to be deficient in vitamins A and D and in calcium and phosphorus[104] However rheumatic fever has occurred with great frequency in naval and other military installations among young recruits who were well nourished and properly fed It is improbable that nutrition is either an essential or important factor in the development of rheumatic fever However it may be a nonspecific factor in determining resistance to infection

Rheumatic fever has been related to relative adrenal cortical insufficiency Kelley et al[7] observed an elevation of cortical steroids early in the acute phase presumably in response to stress with subnormal levels later in the attack and even during the inactive period Animal experiments suggested that the adrenal cortical insufficiency preceded

rather than resulted from the rheumatic fever

Physical Factors Trauma

Frequently the localization of rheumatic arthritis is determined by physical strain Thus the joints of the lower extremities are more apt to be affected when the patient s occupation demands excessive walking or standing the joints of the hands may be involved among typists or seamstresses

The French school of physicians repeatedly emphasized the importance of trauma in determining the onset or recurrence of rheumatic fever The most striking instances are those in which within a few days after a fall or other injury acute rheumatic fever develops first in the joint nearest to the injured region [43] The factor of coincidence is difficult to exclude

PATHOLOGY

GENERAL FEATURES

Pathologically rheumatic fever is characterized by *proliferative* and *exudative inflammation* involving primarily collagen tissue or its ground substance There is a pronounced tendency to affect tissues lined by endothelium including blood vessels endocardium pericardium and synovia

The *primary rheumatic lesion* is characterized by swelling and occasional necrosis of collagen or of the ground substance between the collagen fibrils This undergoes a hyaline or eosinophilic alteration termed fibrinoid degeneration Klinge[74] refers to this early change as the rheumatic fruh infiltrat ' in analogy with tuberculosis but the use of this expression in rheumatic fever may be confusing The swelling of collagen is associated with an exudative reaction consisting of edema lymphocytes and other round cells, and less characteristically of polymorphonuclear and plasma cells Recent studies indicate that the early fibrinoid change which was thought to represent degeneration of collagen, is actually material deposited in the ground substance between the collagen fibers [1] Chemical studies have indicated that the fibrinoid is resistant to collagenase, whereas it is susceptible to tryptic digestion suggesting its protein nature The fact that fibrinoid stains with Schiff s reagent after periodic acid oxidation suggests that it contains mucopolysaccharides The precipitated fibrinoid may result from the interaction of acid mucopolysaccharides and alkaline protein material from plasma or necrotic tissue or both The possible relation of the mucopolysaccharide, hyaluronic acid, to rheumatic fever has been mentioned

The *proliferative reaction* is characterized by granulomatous formations which in their most characteristic form are called Aschoff bodies (infra) This proliferative phase is often so dominant that Fahr[14] refers to rheumatic fever as rheumatic granulomatosis The proliferative reaction consists of focal (Aschoff bodies) or diffuse cellular collections including numerous round cells macrophages fibroblasts and peculiar large cells which may be multinucleated The exudative and proliferative reactions are not sharply demarcated both occurring simultaneously in varying intensity

The *final stage of rheumatic inflammation* is characterized by healing and scar formation In the valves such scarring results in serious deformities The above-mentioned exudative and proliferative inflammatory lesions represent the *active stage* of rheumatic fever In the *inactive stage*, the inflammatory reaction is absent and only the healed scars are observed

CARDIAC LESIONS

Localization of Rheumatic Lesions

Rheumatic cardiac lesions are characterized by their widespread distribution in the endocardium, myocardium, pericardium and conduction system This is the basis for the term *rheumatic pancarditis* The detailed studies of Gross and his associates on rheumatic lesions in their numerous sites of localization have provided an extensive anatomic armamentarium with which to establish the essential rheumatic nature of cardiac disease even in the absence of Aschoff bodies or a typical clinical history of rheumatic fever

Specific and Non specific Lesions

The *specific lesions* are the Aschoff bodies which are described in the next section It is generally agreed that the presence of myocardial Aschoff bodies is definite evidence of rheumatic heart disease " " The granulomatous lesions described as occurring in animals following various experimental efforts to produce rheumatic fever do not show the specific characteristics of the Aschoff bodies

The *non specific but rather characteristic*

lesions include the macroscopic and microscopic alterations in the left atrium, the vascularization and inflammation of the valves (including the valve rings), the valvular verrucae the valvular deformities the pericardial lesions, myocardial scars and certain lesions at the root of the aorta and pulmonary artery

Some lesions are very characteristic if not specific Among these may be mentioned the banded appearance and palisade formation of the cellular exudate in the left atrial endocardium the subendocardial reduplications in the left atrium and valve and the vascular lesion termed the intimomusculoelastic variety

The Myocardial Aschoff Body

Aschoff bodies are rounded or spindle shaped submiliary nodules of microscopic size Rarely conglomerations of Aschoff bodies form grossly visible nodules which appear as pearly white streaks They occur in any portion of the heart, but most often in the subendocardial regions of the left ventricle and frequently in close proximity to small blood vessels They primarily involve the interstitial tissue

The structure of the Aschoff body undergoes a life cycle corresponding with the clinical course of the disease [64] The earliest development representing a pre Aschoff body stage is characterized by swelling and fibrinoid degeneration of the interstitial ground substance and local accumulations of small round cells apparently lymphocytes At this stage argentophilic fibers can be demonstrated by Pap s stain between the swollen collagen fibers and close to the round cells At this stage also the lesion is not specific for rheumatic fever and this must be kept in mind in the evaluation of similar experimental lesions

The typical specific Aschoff body presents certain definite features

(1) There are characteristic cells with abundant somewhat basophilic cytoplasm and irregular boundaries (ragged edges) The cytoplasm may appear as irregular broken syncytial masses of indefinite outline

(2) Many of these cellular nuclei have an owl eye or ' target appearance The nuclei are of circular shape with deeply staining nuclear membrane and a dark sometimes stellate (wheel spokes) nucleolus

(3) There are multinucleated giant cells with usually two or three and occasionally seven or more round or oval nuclei situated in the center of the cell There has been disagreement as to whether these multinucleated cells of the Aschoff body are derived from non myogenic mesenchymal cells or from injured myofibrils [88] According to the recent studies of Wagner and Tedeschi [140] giant cells may arise from either source but the mesenchymal giant cell is specific for rheumatic fever whereas the myogenic giant cell is non specific and may be found also in a variety of other diseases such as giant cell myocarditis, lupus erythematosus and polyarteritis

(4) Other cells within the Aschoff body proper resemble the fibroblast or fibrocyte while still others are small cells with large solidly staining polymorphous nuclei (pyknotic cells)

(5) Among the characteristic owl-eyed giant fibrocytoid and pyknotic cells is swollen collagen or ground substance which has become disintegrated and granular Silver impregnation reveals argentophilic fibers

(6) The Aschoff body proper composed of the above elements is usually surrounded by a mantle of polymorphonuclear cells lymphocytes plasma cells fibroblasts or occasional eosinophils

While the above elements are always present their relative proportions and their figurative arrangement undergo variations according to the acuity or chronicity of the disease the looseness or compactness of the affected tissues and perhaps also according to the immunologic state of these tissues Eventually the Aschoff body is converted into a characteristic spindle shaped flame-shaped or triangular scar lying between the muscle bundles and surrounding blood vessel [4]

Aschoff Bodies in Resected Left Atrial Appendages

Aschoff bodies have been found in 16 to 74 per cent (average 33 per cent) of the atrial appendages which were removed in the course of operations for mitral stenosis Among the larger series of case Decker et al [27] reported the presence of Aschoff bodies in 83 of 183 appendages (45 per cent) and Tedeschi et al [139] in 75 of 400 appendages (18 8 per cent) It is a striking fact that although the Aschoff body has always been regarded as denoting *active* rheumatic fever it has not been possible to correlate the finding of Aschoff bodies in the atrial appendages with

clinical or laboratory evidence of active rheumatic fever [90] In fact, patients with any manifestations suggesting the possibility of rheumatic activity were not subjected to operation Studies of autopsy material disclosed that the findings in the removed appendages were representative of the findings elsewhere in the heart The patients with Aschoff bodies in their atrial appendages disclosed no greater tendency to postoperative rheumatic recrudescence or to an increase in operative mortality or morbidity than those whose atrial appendage showed no Aschoff bodies [17]

It is apparent that the Aschoff body cannot be regarded as an invariable sign of clinically active rheumatic fever This apparent change in concept can probably be explained by attention to the life cycle of the Aschoff body, as stressed by Gross and Ehrlich [84] Accordingly one should distinguish between active and healed Aschoff bodies [130] By careful histologic (and histochemical) studies of 400 consecutive left atrial appendages removed at mitral commissurotomy in patients with clinically inactive rheumatic fever, in 75 of which Aschoff bodies were found, Tedeschi et al [130] determined that evidence of active rheumatic carditis was present in only 8 In the remaining 392 cases (98 per cent) only healed or healing lesions were noted In 67 of the 75 cases with Aschoff bodies, the Aschoff bodies were senescent, i e healed Thus the Aschoff body, pathologically, may be active or healed It is not always invariably indicative of clinical rheumatic activity It may denote such activity only when careful study of its life cycle reveals that the Aschoff body is in its 'active' or "juvenile stage

Pericardial Lesions

Pericarditis is one of the most frequent and most characteristic of rheumatic lesions The occurrence of acute pericarditis and of adherent pericardium was described by Baillie[5] and other early writers The typical reticulated, curdled appearance of fibrinous pericarditis was described by Corvisart and Laennec the latter noting its similarity to "bread and butter" an expression retained by Hope and all textbook writers after him Gross lesions are almost invariably present either diffusely or as localized patches of fibrous thickening

In the *active cases* there may be a universal fibrinous exudate with thickening glazing and adhesions There is a variable amount of straw colored, turbid fluid containing many shreds of fibrin Occasionally the effusion is fibrinopurulent With recurrent attacks the pericardium is converted into a thick shaggy membrane with numerous tenuous adhesions In the *inactive cases* the pericardial layers are thick and adherent to each other and to neighboring extracardiac structures Frequently there is complete obliteration of the pericardial sac but in the early stages there may still be serofibrinous or serohemorrhagic exudate sacculated between adhesions Calcification may occur Occasionally, there are peculiar polypoid and cystlike formations

Microscopically, pericardial lesions are found in almost 100 per cent of the *active cases* [4] The earliest lesions are represented by swelling and degeneration of collagen and ground substance in the lamina propria inflammation and vascularization of the same layer and of nearby portions of the subjacent adipose layer Soon there is an exudation of fibrin which together with the subjacent inflammation, represents the non-specific reaction of a serous membrane to an injury The mesothelial cells may become completely desquamated and may form pseudo-gland structures or polyps With recurrent infections and in later stages of the active cases there is marked thickening of the pericardial membranes with layers of fibrin inflammatory exudate and granulation tissue The pericardial layers become adherent and the pericardial cavity is obliterated

In the *inactive cases* the pericardial layers are thickened and adherent owing to the formation of considerable fibrous tissue There may be inflammatory residua consisting of infiltrations of small round cells in the deeper layers of the lamina propria and adjacent layers and an increased number of vessels showing structural changes

Rheumatic Lesions in the Left Atrium

Detailed descriptions have been reported by MacCallum[83] and by Gross[57] (see p 817)

Macroscopic Appearance The characteristic lesions are usually situated on the posterior wall of the left atrium just above the posterior cusp of the mitral valve They consist of an irregularly raised series of ridges and mounds forming tawny gray patches, or occasionally flat yellow plaques In the *inactive* stage the lesions become grayer and more translucent and the endocardium may appear

wrinkled There may be hyaline plaques occasionally with lime Macroscopic lesions in the left atrium are reported to occur in 29 to 80 per cent of rheumatic hearts the higher percentage in the active cases Massive calcification of the left atrium may be observed in cases of rheumatic heart disease with a long history of atrial fibrillation and congestive heart failure [113]

Microscopic Appearance The atrial endocardium becomes widened by edema and cellular infiltration The collagen and interstitial ground substance undergo swelling and degeneration and assume a banded appearance The various inflammatory cells are often oriented characteristically at right angles to the atrial lumen and may be palisaded in layers along the bands of swollen collagen The normal avascular endocardium becomes highly vascularized by the penetration of capillaries at right angles from the subendocardial layer

The *inactive or healed lesion* consists of pronounced widening of the atrial endocardium by fibrous tissue A considerable portion of the thickening is due to characteristic endocardial reduplications [14] composed of newly formed layers of tissue arising from the normally inconspicuous subendothelial mesenchyme These wide reduplications are demarcated by condensations of elastic tissue each one representing an individual attack of rheumatic fever

Lesions of the Valves

Rheumatic valvular lesions have been described in detail by Coombs [8] Swift [17] Gross and Friedberg [46] and others

Active Stage The most frequent lesion is the thickening of the valve cusp and its loss of transparency The most characteristic lesion is the vegetation or verruca ' The verrucae appear as rows of fine glistening grayish or yellow wartlike vegetations on the closure line of the mitral and aortic and much less commonly on the tricuspid or pulmonic valves in the given order of frequency Not infrequently the tricuspid leaflets and occasionally the pulmonic leaflets disclose distinct microscopic lesions when they appear normal on gross examination The normally concave scalloped margins of the atrioventricular valves are thickened and straightened The atrial surface may show gross vascularization

Microscopically the earliest valvular lesions occur at the ring ' or attachment of the cusp to the fibrous annulus [17, 46] The close anatomic relationship of the four fibrous annuli to each other accounts for the ease of extension of the inflammatory process from one ring to the others The ring becomes vascularized and swollen with edema and inflammatory cells The inflammatory process extends throughout the cusp and produces a valvulitis before there are verrucae [50] The typical rheumatic proliferative and exudative lesions occur The cusp becomes thickened by edema capillary vascularization and cellular infiltration (lymphocytes predominantly and occasionally polymorphonuclear leukocytes but Aschoff bodies fibroblasts macrophages and plasma cells also occur)

The verrucae in active cases consist of hyaline eosinophilic material resulting from swollen degenerated collagen and disintegrated cells near the surface of the valve The verruca arises chiefly from swollen degenerated valvular substance which is extruded beyond the surface of the cusp However platelet thrombus and a small amount of fibrin arising from the blood stream may be deposited as a cap on the valvular component of the verruca According to Tweedy [126a] the high incidence of these thrombotic deposits rather than the valvulitis or degenerated collagen is responsible for valvular thickening and fusion of chordae tendineae

Inactive or Healed Stage (see chapters on individual valvular lesions)

Lesions of the Coronary Arteries and Their Branches

Lesions of the vascular apparatus including the coronary arteries represent a fundamental feature of the pathology of rheumatic fever [121, 55] but it is doubtful whether they are of sufficient importance to account for clinical phenomena The usual evolutionary degenerative changes in the coronary vessels are accelerated and intensified in cases of rheumatic fever therefore coronary atherosclerosis may occur much earlier in such cases This is exemplified by a seventeen months old child whom I observed with acute rheumatic fever whose heart at postmortem examination disclosed a complete thrombosis of a major coronary artery

There may also be non specific degenerative or inflammatory lesions which are occasionally grossly visible in the small myocardial arteries but which are more often of micro

scopic size. The gross lesions may be those of polyarteritis nodosa[41] while the microscopic lesions consist of intimal proliferation and necrosis, endarteritis verrucosa or polyposa, or fibrin like occlusions which become organized and recanalized.[139] Gross, Kugel and Epstein[57] described intimo musculo elastic lesions of the small coronary arteries characterized by intimal proliferation of smooth muscle and elastic tissue and considered almost specific for rheumatic fever.

Lesions in the Aorta and Pulmonary Artery

Klotz[7] gave the first detailed descriptions of rheumatic vascular lesions including those of the aorta. Pappenheimer and von Glahn,[93] Gross[53] and others also contributed studies of rheumatic aortic lesions. Occasionally there are macroscopic brownish ridges or plaques on the inner surface. The usual lesions at the root of the aorta are microscopic and situated chiefly in the outer portion of the media and in the adventitia following the course of the vasa vasorum. There are collections of lymphocytes, polys and Aschoff bodies, edema, pronounced capillarization and scarring and disruption of the elastica. Similar lesions are also found occasionally in the pulmonary artery and have been described by Paul,[99] Chiari,[16] and others.

Lesions in the Atrioventricular Conduction System

The frequent occurrence in rheumatic fever of arrhythmias and especially of partial heart block may be due in many instances to anatomic lesions in the conduction system. Gross and Fried[5] found exudative or vascular lesions within the bundle of His or surrounding tissue in 66 per cent of active cases.

EXTRACARDIAC LESIONS IN RHEUMATIC FEVER

Subcutaneous Nodules

Pathologically these are proliferative lesions consisting of collagen swelling and degeneration, inflammatory cells, edema and vascularization similar to that in other rheumatic lesions.[89] Often there is a necrotic center containing fibrinoid material. Structures resembling Aschoff bodies have been reported. The nodules may show scarring, calcification and rarely deposition of cartilage or bone. Allowing for the difference in milieu, the subcutaneous nodule corresponds in structure and specificity to the Aschoff body. Some investigators have reported histologic resemblances to the nodules found in rheumatoid arthritis,[26] but I believe there are essential pathologic differences.[70]

Pulmonary and Pleural Lesions

Pulmonary and pleural lesions occur frequently in rheumatic fever, but there is disagreement as to the specificity of a rheumatic pneumonia.[100, [illegible], 8]

The lungs have been described as characteristically large, purplish red, beefy and of india rubber consistency.[illegible] The involved areas are non friable and homogeneous and present atelectasis and splenization rather than hepatization. *Microscopically*, the affected parts show edema and hyperemia, *local* atelectasis and widespread focal hemorrhagic lesions involving lobules or groups of lobules.

The alveolar walls are thickened by proliferating capillary endothelial cells and fibroblasts, and the interstitial tissue is thickened by edema and inflammatory and mononuclear cells.

The alveolar lumina are filled with edema fluid and frequently by a hemorrhagic and fibrinous exudate. Mononuclear cells predominate and include desquamated epithelial cells and phagocytic cells.

Vascular lesions of the capillaries and small arteries consist of intimal thickening, hyaline thrombi, occasional scarring or necrosis of the media and adventitial and periadventitial cellular infiltrations.

A hyaline membrane lining the bronchioles and alveolar ducts is a characteristic feature, and possibly represents a *transformed* fibrinous exudate.[illegible]

A fibrinous or serofibrinous pleural exudate may be present. Proliferative and exudative "rheumatic like" lesions have been described, but no definite Aschoff bodies have been demonstrated.

Other Lesions in Rheumatic Fever[illegible]

Abdominal pain may be related to necrotizing arteritis of visceral arteries[41] *or other* vascular lesions. Serous peritonitis with vascular lesions and inflammatory exudate in the subperitoneal tissue has been described by Rhea[109] in fatal cases of rheumatic fever. Specific rheumatic lesions have been reported in the peritonsillar tissue[47] and in the regional lymph nodes draining rheumatic tissues.[40]

Cerebral lesions associated with chorea include a disseminated meningoencephalitis affecting chiefly the corpus striatum.[49] A meningoencephalitis has also been reported in rheumatic heart disease without *chorea*.[44]

Bruetsch[9] has repeatedly reported and emphasized the occurrence of cerebral lesions and cerebral sequelae of rheumatic fever In particular, he observed a "rheumatic obliterating arteritis involving the small meningeal and cortical vessels with consequent infarction and softening of cerebral tissue Certain cases of mental illness and epilepsy were attributed to such rheumatic cerebral lesions

RELATION OF RHEUMATIC FEVER TO RHEUMATOID ARTHRITIS

There are many differences between the clinical manifestations and course of rheumatic fever and of rheumatoid arthritis chief of which is the frequency of cardiac involvement in the former In recent years necropsy findings have been reported which suggest that cardiac lesions of rheumatic fever are encountered with significant frequency in cases of rheumatoid arthritis [6 10] although there are also contrary reports[31] Rosenberg and associates[11] recorded the finding of rheumatic heart disease in 16 (53 per cent) of 30 autopsied cases of rheumatoid arthritis and Young and Schwedel[149] in 25 (66 per cent) of 38 such cases In evaluating these reports it is important to know the exact criteria employed for the diagnosis of rheumatic heart disease and the incidence of such ' rheumatic lesions in control groups Thus according to criteria used by Hall and Anderson[44] rheumatic stigmata in presumably normal hearts were found microscopically in 90 per cent of 112 hearts and Aschoff bodies in 30 per cent of the hearts If such criteria are employed the finding of rheumatic lesions in cases of rheumatoid arthritis loses significance In general there appears to be a definite distinction between the pathologic lesions usually associated with rheumatic fever and those of rheumatoid arthritis[6] The clinical course and electrocardiographic findings in rheumatic fever are not observed with rheumatoid arthritis In the course of observing several hundred patients with rheumatoid arthritis over many years I have only once observed the appearance of rheumatic cardiovalvular disease (aortic insufficiency) in later adult life

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Chapter 32

RHEUMATIC FEVER

Clinical Picture

INTRODUCTION

The clinical picture of rheumatic fever may be dominated by cardiac or extracardiac symptoms. But even when the obvious symptoms are extracardiac one can almost always assume the probability of cardiac involvement. The most characteristic clinical picture of rheumatic fever is that of an acute migrating polyarthritis with fever and other evidences of toxemia. But especially in children, the clinical picture may be dominated by extra-articular manifestations including chorea, abdominal pain, cutaneous and subcutaneous lesions and cardiac disease. Atypical, mild and subclinical forms of rheumatic fever are not uncommon among both children and young adults.

Rheumatic fever is characterized by its chronicity and tendency to recurrent exacerbations. The recurrences, like the original attack, consist of any one of the variety of clinical forms which rheumatic fever may assume. Thus the first attack may be one of chorea, the second polyarthritis and the third pancarditis. Or cardiac disease may be present from the beginning, each new attack leading to further myocardial and valvular damage. The acute attacks generally last one to three months but occasionally there are fulminating cases ending fatally in several days or weeks. Usually the disease enters a chronic afebrile stage in which there may be no symptoms unless an acute exacerbation occurs.

Rheumatic heart disease is considered as being *active* or *inactive* depending on the persistence or subsidence of acute rheumatic inflammation. This distinction is important in the management of the patient and the evaluation of his prognosis. As in tuberculosis inactive rheumatic heart disease is not synonymous with cure, for there is a great tendency to recurrence of the active disease. The symptoms of active rheumatic heart disease are due to the inflammatory lesions in the heart and the associated toxemia. The symptoms of inactive heart disease are due to the scars and deformities produced by healing of the inflammatory lesions and to the associated chemical changes in the myocardium. These alterations may be insufficient to produce clinical symptoms during long intervals of the inactive stage.

MODES OF ONSET

The onset may be insidious or acute. Vague prodromata may precede the acute outbreak. Characteristically a hemolytic streptococcal sore throat, tonsillitis or scarlet fever is followed by a latent period of one to four weeks after which symptoms of rheumatic fever appear. Following are some of the more common ways in which rheumatic fever and rheumatic heart disease begin.

1. *Arthritis and fever* are the commonest symptoms of onset. Occasionally there is no definite arthritis, but only fleeting multiple joint pains without noticeable inflammation or pain and disability involving a single joint.

2. *Cardiac symptoms* may first attract attention to the patient's illness. The chief complaint may be precordial pain due to a fibrinous pericarditis or a pericardial effusion, or else there is palpitation resulting from tachycardia and extrasystoles. Occasionally dyspnea, edema, abdominal distress and other symptoms of myocardial failure appear to be present from the beginning.

3. *Chorea* may be the first and sole evidence of the initial attack of rheumatic fever. Occasionally this follows a physical or psychic trauma. Cardiac lesions and other rheumatic

symptoms may develop concomitantly with this initial attack or more often in subsequent rheumatic episodes

4 *Abdominal and gastrointestinal symptoms* Vague fleeting abdominal pains are uncommon prodromal symptoms of rheumatic fever Occasionally the abdominal pain is severe and simulates an acute surgical complication

5 *Fever of obscure origin* associated with malaise headache or anorexia may be present for some weeks before other evidences of rheumatic fever appear

6 Rheumatic heart disease may be *latent* its recognition depending on discovery of a valvular lesion at routine physical examination Or cardiac failure may develop in an individual who gives no history of rheumatic fever The rheumatic etiology of the failure is suggested by the finding of evidence of valvular disease

7 Rarely the first symptoms of rheumatic fever are subcutaneous nodules, cutaneous lesions such as erythema marginatum or profuse epistaxis

Non specific prodromata have been mentioned as preceding the well defined symptoms particularly in children The symptoms in the prodromal stages of rheumatic fever include pallor fatigability anorexia, digestive disturbances abdominal pain loss of weight nervous irritability so-called growing pains in the joints and adjacent muscles and tendons respiratory infections adenopathy and low grade febrile attacks

CLINICAL FORMS OF RHEUMATIC FEVER

The lesions of rheumatic fever may affect almost every organ Correspondingly the clinical symptoms and combinations of symptoms are remarkably protean However certain common clinical forms of the disease may be distinguished according to the predominant symptoms As the disease becomes prolonged or acute exacerbations ensue these clinical forms tend to intermingle

1 The *articular form* is the most distinctive and the most easily recognized Fever and arthritis may occur after a free interval of one to three weeks following an upper respiratory infection The onset of fever and polyarthritis may be more gradual the temperature rising as the inflammation spreads from joint to joint until many of them have been successively involved When fully developed the clinical picture is that of a general infection with toxemia chilliness (or occasionally rigors) and severe sweats but the acute migrating polyarthritis is the dominant feature

2 The *cardiac form* is the most serious clinical variety of rheumatic fever It is especially frequent in children The illness may present any one of the modes of onset listed above but evidences of cardiac disease rapidly dominate the clinical picture Fever and other signs of infection are present Frequently there are symptoms of fresh pericarditis or pericardial effusion The heart becomes enlarged Evidences of left and right heart failure may become prominent Valvular disease may develop under observation or may represent residua of a previous attack Joint symptoms cutaneous lesions pulmonary disease are overshadowed by the pancarditis Cardiac failure may subside and recur with renewal of the infection Death may result occasionally If the patient recovers he is left with an enlarged heart badly functioning valves an injured myocardium and pericardial adhesions

3 The *typhoidal* or *influenzal form* embraces the cases in which fever and toxemia are the dominant features The patient may be mistakenly treated for grippe pneumonia or typhoid fever Fever of obscure origin may be the only evidence of a recurrent bout of rheumatic fever and particularly of a reactivation of rheumatic carditis

4 The *pulmonary form* refers to cases with predominant pleural and pulmonary symptoms Fever generally of high degree is invariably present Pericarditis and other cardiac symptoms are usually and extra cardiac symptoms are sometimes associated

5 The *abdominal form* Occasionally abdominal and gastrointestinal symptoms not only initiate the rheumatic attack, but continue as its essential features

6 *Chorea* may be classified as a *neurologic form* of the disease Its rheumatic nature is denoted by the later development of other classic features of rheumatic fever in one half to three quarters of the cases of chorea

Atypical Forms in Young Adults

Observations during World War II and subsequently disclosed the relative frequency of rheumatic fever among young adults in the military forces[78, 89, 102] Usually the clinical picture was characterized by fever and an

acute polyarthritis Not infrequently, however, there was only mild pain and stiffness in a single joint, without systemic symptoms, or there were only chills and fever, or vague muscular pains backache and urinary symptoms or abdominal and gastrointestinal symptoms In some of these reported cases, one may question the diagnosis of rheumatic fever despite electrocardiographic abnormalities (See also p 843)

GENERAL COURSE OF RHEUMATIC FEVER

In general the course of rheumatic fever may be classified under four general types

1 The *recurring type* is characterized by an acute attack which subsides in one to six weeks in mild cases or in six weeks to four months in severe cases Subsequently there is complete inactivity for one or more years *After two to five such attacks, the disease remains inactive* This is the most common form

2 The *chronic active type* in which there are troughs of relatively little clinical activity but in which there is never complete subsidence From time to time there are clinical exacerbations Progressive cardiac failure leads to fatality after many months or after several years

3 The *chronic inactive type* in which carditis is part of the initial attack but there is no recurrence of activity thereafter

4 The *acute fulminating type* is uncommon and is characterized by high fever and toxemia with severe carditis and heart failure and a fatal issue after several weeks or months

THE INDIVIDUAL FEATURES OF RHEUMATIC FEVER

These are classified as (1) general, non specific evidences of infection and (2) local manifestations which are more characteristic and depend on the involvement of numerous individual organ systems

GENERAL SYMPTOMS

The general symptoms may be very vague particularly in the prodromal period and in children The affected child tires easily, appears pale and listless eats little, loses weight and seems to be wasting He may be brought to the doctor because of "nervousness" pallor and undernutrition, poor schoolwork, or because it is feared he is suffering from pulmonary tuberculosis When the disease is well defined, there are distinct symptoms of a general infection

Fever

This is an almost constant symptom except in chorea It is the most practical and reliable guide to persistence of infection when the local symptoms have disappeared The temperature curve is rather variable but four general types may be mentioned (1) an irregular well marked febrile course lasting from a week to three or four months, (2) a continuous low grade febrile or subfebrile course, (3) a continuous low grade curve accentuated by more definite bouts of fever lasting several days, (4) an infrequent hyperpyrexia which has been virtually eliminated since the introduction of salicylates

The temperature usually ranges up to 103° F, occasionally higher, with daily variations of 1° to 3° F Before the use of salicylates characteristic types of the fever curve were described Friedlander[7] described monocyclic, polycyclic and continuous varieties In the "monocyclic" variety which composes about 60 per cent of cases, there is a progressive steplike rise in temperature lasting about a week each elevation corresponding to the involvement of new joints As the inflammation involves new joints it subsides in the original sites which are not implicated again *The* temperature falls gradually when no *further* joints are affected In the "polycyclic" variety, cycles such as that described come and go with relapses, the same or new joints being involved *The course is more severe and more* prolonged than in the monocyclic variety, pericarditis, pneumonitis and *heart failure* are common In the "continuous" *temperature* curve there is a prolonged irregular elevated temperature

The duration of the fever is quite variable Gull and Sutton[85] using only mint water to treat their cases concluded that the average duration of uncomplicated rheumatic fever was nineteen days Pribram[70] reported that of 457 cases treated with and without salicylates 27 per cent had fever for two to three weeks 16 per cent for three weeks or more and 3 per cent for more than thirty days *In the remaining,* 54 per cent the duration of fever in a single acute attack was less than two weeks The entire illness generally lasted one and one half to two times as long as the fever The ad

ministration of salicylates reduced the temperature but not the duration of the attack, which ranged between 14 7 and 47 5 days Similarly, Miller[60] found an average duration of 33 days in 3500 cases of rheumatic polyarthritis the period being the same whether or not salicylates were administered

Persistence of Activity without Fever Fever is an almost invariable accompaniment of active rheumatic disease However occasionally the temperature is normal despite the presence of active infection In chorea, which is generally accepted as a manifestation of active rheumatic fever the temperature may remain normal throughout the attack In the prearthritic or precardiac stages of rheumatic fever there is often no fever although progressive anemia fatigability loss of weight, etc, indicate active disease Similarly there may be no fever toward the end of a rheumatic attack when all symptoms have disappeared yet there may be persistent rheumatic inflammation as indicated by tachycardia leukocytosis and increased rate of sedimentation of red blood cells There may be little or no fever with subcutaneous nodules although these represent active rheumatic disease Thus while fever is a valuable guide to rheumatic inflammation its absence is not conclusive that activity has subsided

Pulse

A regular tachycardia of 100 to 140 is a common sign of rheumatic activity The tachycardia is often out of proportion to the degree of fever The pulse is full, bounding easily compressible and often dicrotic In convalescence there may be bradycardia When the temperature has reverted to normal either spontaneously or with salicylates a persistent tachycardia usually indicates continued rheumatic activity probably within the heart

Sweating

Profuse sweating has been described as a characteristic feature, particularly of the articular form of the disease In recent years this manifestation has appeared to be less prominent

Loss of Weight and Undernutrition

These are frequently present in the prodromal stages of the initial and subsequent attacks Weight curves especially in children are valuable guides to the progress of the rheumatic patient and to the persistence of active inflammation

LOCAL SYMPTOMS

The numerous symptoms of rheumatic fever are evidence of widespread involvement of many organs The most characteristic symptoms are due to lesions of the heart (pancarditis), the joints (arthritis) the skin (subcutaneous nodules) and the nervous system (chorea) But almost every organ may be affected, as shown by the widespread vascular lesions described Many of the lesions, however, fail to cause obvious symptoms

Of 1108 rheumatic patients under the age of 12 seen in a first attack carditis was present in 61 per cent arthritis in 57 per cent, chorea in 56 per cent and subcutaneous nodules in [illegible] per cent [illegible] In a similar series observed by Coombs[20] in an outpatient department, 72 5 per cent showed cardiac disease 61 [illegible] per cent arthritis, 47 2 per cent chorea, and 4 per cent subcutaneous nodules Coburn[16] listed the frequency of various symptoms in 162 patients presenting the "rheumatic state as follows

	Per cent
Polyarthritis	85
Pancarditis	65
Recurrent epistaxis	48
Muscle (growing) pains	47
Attacks of pallor	36
Severe headaches	33
Cardiac pain	3[illegible]
Chorea	[illegible]
Abdominal pains nausea vomiting	20
Erythema marginatum	17
Subcutaneous nodules	13 6

These and other statistical analyses indicate the great frequency of cardiac disease in rheumatic fever Because of its frequency and seriousness as compared with other symptoms cardiac disease is the central feature of any consideration of that disease Our presentation of individual symptoms is therefore concerned essentially with cardiac manifestations Extracardiac symptoms are presented primarily from the point of view that they may be the earliest or most prominent clues leading to the diagnosis of rheumatic heart disease or to the detection of a reactivation of rheumatic cardiac infection

Cardiac Symptoms

Rheumatic cardiac symptoms are classified according to their occurrence in the (a) *active* or (b) *inactive* stage of the infection They are further classified according to the anatomic site of the lesions into (1) *endocardial* and *valvular,* (2) *myocardial* and (3) *pericardial* manifestations

It should be noted that in both the active and inactive stages cardiac lesions may be present without producing overt symptoms The latter depend on the extensiveness of the anatomic lesions and their situation in critical cardiac sites In the absence of symptoms or a history of rheumatic fever, rheumatic heart disease is discovered accidentally on physical examination or sometimes for the first time at postmortem examination [] Occasionally the presence of rheumatic heart disease is first disclosed when the patient is observed because of the development of atrial fibrillation, congestive heart failure or bacterial endocarditis

Active Stage of Rheumatic Heart Disease

1 *Endocarditis and valvulitis* The development of endocarditis may be documented by (1) an alteration in cardiac sounds, (2) the occurrence of new cardiac murmurs and (3) a change in the character of murmurs previously present [, 101] But there may be no specific evidence of valvular involvement during the acute attack

Very early there is a loss of the distinctive muscular quality of the first sound at the apex It may become prolonged and diminished in intensity It has been described as "impure" "murmurish" or "mushy" Sometimes there is a splitting or reduplication of the second sound at the apex an occurrence emphasized by Sansom[8] and Cheadle[] A loud third sound is common during the acute attack [90] In fact a triple rhythm usually due to a loud third heart sound occasionally to gallop rhythm, is a frequent finding in acute rheumatic fever

Blowing systolic murmurs occur early and frequently They are located at the apex to the left of the sternum at the level of the fourth rib, over the pulmonic or aortic area or over an extensive precordial area They are best heard when the patient is supine These systolic murmurs may indicate early organic involvement of the valvular endocardium, but must be distinguished on the one hand from functional murmurs due to the associated fever or anemia, or cardiorespiratory factors, and on the other hand from the organic murmurs of chronic valvular deformity which evolve later in the course of the disease [68] The early systolic murmur may completely disappear with subsidence of the active stage of the disease

Occasionally a mid-diastolic apical murmur has been reported as occurring in the early stages of rheumatic fever and disappearing after the rheumatic attack abates [] This should not be confused with the diastolic murmur of mitral stenosis [55] The apical mid diastolic or presystolic murmur of acute rheumatic fever has been explained as due to relative mitral or tricuspid stenosis secondary to dilatation of the left or right ventricle [101] This explanation is unclear, but relative mitral stenosis may be due to increased speed of blood flow Phonocardiography may be necessary to distinguish a crescendo-type of first sound, a loud third sound or gallop rhythm, which may simulate an apical presystolic or mid-diastolic murmur [1, 57, 8] Subsequently, organic murmurs of chronic valvular disease may or may not develop Sometimes signs of organic valvular disease develop early in the course of what appears to be the first active stage of the disease In such instances one is at a loss to determine whether these signs are the result of a previous unnoticed attack or whether they can develop with unusual rapidity in the course of the first one

2 *Pericarditis* In the active stage two clinical varieties of pericarditis may be distinguished[93] (1) *acute fibrinous pericarditis* and (2) *pericarditis with effusion*

Postmortem studies disclose that organization of the inflammatory exudate and the development of adhesions occur even in the active stage but these give no clinical symptom in the active disease (p 818) The incidence of clinical pericarditis in rheumatic fever is variously reported as 3 per cent [76] 5 per cent [] and 13 per cent [20] and 5 to 10 per cent in the *recent cooperative study* of cases in the United Kingdom and the United States [] Pericarditis is often overlooked clinically unless frequent and careful examinations are made Recent pathologic studies indicate microscopic pericardial lesions in almost 100 per cent of patients dying of active rheumatic heart disease but clinical evidence were reported only when the lesions were severe and extensive [5]

When there is clinical evidence of pericarditis, the patient is usually suffering from a serious form of rheumatic heart disease The recognition of pericarditis should call attention to the underlying myocardial infection Pericarditis is also associated with other serious visceral rheumatic infections, particularly pleurisy and pneumonia Subcutaneous

nodules are said to be associated frequently when there is pericarditis

(1) ACUTE FIBRINOUS PERICARDITIS The essential symptom is substernal, precordial or abdominal pain and the essential sign a pericardial friction rub The rub is usually heard for four days or less but occasionally for longer periods A detailed discussion of the symptoms and signs of acute fibrinous pericarditis is presented in Chapter 22

The occurrence of acute pericarditis is often marked by a rise sometimes considerable in the fever curve In young adults in the army signs of pericarditis usually developed within a few days after the onset of acute rheumatic fever Evidence of pneumonia, pleurisy pulmonary infarction or heart failure often accompanies pericarditis

(2) PERICARDIAL EFFUSION of slight degree is generally associated with acute pericarditis

The precordial pain and pericardial rub of the acute fibrinous pericarditis may or may not disappear with the formation of a considerable effusion The patient may suffer precordial oppression and a characteristic sense of anxiety Restlessness insomnia delirium and other mental symptoms occasionally occur With large effusions the patient is exceedingly dyspneic and orthopneic so that he must sit upright in bed Tachypnea is a frequent and prominent symptom The patient may become cyanotic or flushed but often he presents an intense pallor The picture of an intensely pale and dyspneic child sitting up anxiously in bed and complaining of precordial pressure and pain is very suggestive of rheumatic pericarditis with considerable effusion Dysphagia aphonia and an irritative cough may result from pressure on the esophagus or recurrent laryngeal nerve The diagnosis may be confirmed radiologically[7] and by pericardial paracenteses A detailed account of the symptoms and signs of pericarditis with effusion is given in Chapter 22

3 *Myocarditis* Lesions of the myocardium proper are the most important cardiac evidences of active rheumatic fever Recognition of these lesions requires frequent regular examinations In the presence of a rheumatic pericarditis or valvular disease one can virtually assume myocardial involvement An unexplained rise in temperature in the course of rheumatic fever is a significant clue suggesting the necessity of careful examination of the heart An increased pulse rate is merely evidence of the general infection But a disproportionate rise in pulse rate or a persistent tachycardia despite a spontaneous or salicylate induced fall in temperature suggests the presence of carditis

The patient s *symptoms* may be few or they may be numerous and severe Precordial pain of variable severity is frequent

The *signs* of active rheumatic myocarditis are visible tumultuous cardiac action changes in heart sounds rapid cardiac enlargement evidences of heart failure disturbances in cardiac rate and rhythm Electrocardiographic changes also denote myocardial involvement

The earliest signs of myocarditis are changes in the quality intensity and pitch of the first sound[48] This becomes dulled muffled or almost obscured It may appear to have the same pitch and quality as the second sound, producing a tic tac or dup dup effect (embryocardia) instead of the normal lub-dup or lub dupt A blowing systolic murmur may be due to myocardial disease inflammation of the valve rings and cusps or to other factors (such as fever and anemia) associated with the rheumatic affection The cardiac impulse is generally diffuse and feeble But when the acute myocarditis is superimposed on a previously damaged heart with chronic valvular disease and hypertrophy the cardiac [illegible] pulse is more apt to be strong and tumultuous

Evidences of right and left heart fail[illegible] are commonly observed in [illegible] forms of rheumatic myocard[illegible] pericardial or pleural [illegible] tribute to the severity of the dyspnea and orthopnea Diastolic gallop [illegible] portant sign of left ventr[illegible] myocarditis during [illegible] fever However a presystolic [illegible] in the absence of heart fa[illegible] duction time is prolo[illegible] is audible It may also [illegible] gush a physiologic [illegible] tachycardia from a [illegible] rhythm When [illegible] failure [illegible] there may be a sub[illegible] children right-sided [illegible] may be predomi[illegible] the [illegible] The patient s extre[illegible] edema the liver [illegible] Hydrothorax develops and [illegible]

may be ascites The patient complains of abdominal distress and nausea and he may vomit Some children present a puffy face as in glomerulonephritis Unexpected weight gain may precede visible edema There may be cyanosis of the lips and fingertips if anemia is not too severe The cervical veins and those of the extremities become distended, and the venous pressure is elevated

Cardiac enlargement may occur rapidly with active rheumatic heart disease if there is severe myocardial involvement and failure The enlargement may be the result of a previous attack It can be interpreted as a sign of activity only if it develops or progresses under observation and if there are other evidences of active rheumatic fever There may be a diminution in cardiac size with subsidence of rheumatic activity and restoration of cardiac compensation [9]

Disturbances of cardiac rhythm are both frequent and valuable signs of rheumatic myocarditis, but usually are discovered only by electrocardiography (p 837)

Inactive Stage of Rheumatic Heart Disease The clinical picture of inactive rheumatic heart disease is essentially that of valvular disease of the heart Proof that the disease is inactive consists of negative observations For practical purposes rheumatic heart disease is considered as being inactive when in addition to the absence of fever tachycardia and other symptoms of active rheumatic infection, the white blood count, rate of sedimentation of red blood cells and repeated electrocardiograms are normal and the serum has no C reactive protein

Subjective symptoms may be entirely absent in the inactive stage of rheumatic heart disease Physical signs, however, are generally well defined Both the physical signs and the subjective symptoms when present are those of chronic valvular heart disease with or without heart failure These are discussed in detail in the chapters on the individual valvular lesions (Chapters 26 to 29) In a series of 2476 persons with rheumatic heart disease rejected by draft boards in five large American cities there were signs of mitral insufficiency alone in 750, of mitral stenosis alone in 750 of aortic insufficiency alone in 208, of aortic stenosis in 72 and of combined mitral and aortic valvular disease in 628 [84]

Complications of Rheumatic Heart Disease The chief complications of rheumatic heart disease are (1) cardiac failure, (2) atrial fibrillation and other arrhythmias, (3) subacute and acute bacterial endocarditis, (4) embolization More rarely there are anginal syndrome with or without coronary sclerosis or occlusion, essential hypertension hyperthyroidism (Graves' disease), Adams Stokes syndrome Many other so-called complications are really essential elements of the rheumatic affection or represent unrelated intercurrent infections (See also individual valvular diseases, Chapters 26–29)

Extracardiac Manifestations

Arthritis Arthritis is the most constant and most conspicuous local manifestation of the disease Characteristically, there is a symmetrical polyarthritis, primarily affecting large joints, with rapid development and subsidence of inflammatory phenomena and successive involvement of new joints as inflammation in the others regresses But in many cases reported among military forces only a single joint was affected [illegible] The joints most frequently involved are the knees ankles shoulders and wrists However, almost any joint may be implicated, including the small joints of the hands and feet the elbows, hips, vertebrae the sternoclavicular and temperomandibular and crico-arytenoid joints, and even the symphysis pubis Trauma and strain sometimes appear to play a role in determining the affected joints

The symptoms vary considerably in severity and consist of pain redness swelling increased warmth of the skin overlying the joint, and disability The acute symptoms, including swelling and effusion *generally respond* remarkably to the administration of adequate doses of salicylates, but there may be a slight persistent residual pain and swelling Inflammation in a given joint may develop fully in a few hours Its subsidence is more gradual requiring between one day and one week and occasionally longer

The synovial fluid is a pale yellow fluid which may be clear or slightly cloudy and may contain some flakes There is an early predominance of polymorphonuclear leukocytes with a few mononuclear cells and undifferentiated young connective tissue cell Later there are numerous clasmatocytes containing degenerated cells and debris [11] Sup-

puration does not occur except by secondary infection with pyogenic organisms

Tendinitis Myositis Tenosynovitis Bursitis. Pain in the juxta articular region may be due to inflammation of neighboring tendons and muscles They are responsible for the growing pains in children which should not be confused with the more significant rheumatic arthritis [16] As I have pointed out with Gross [5] *polymyositis* may occur when periarteritis nodosa is associated with rheumatic fever In *tenosynovitis* of the hand, considerable effusions may occur

Subcutaneous Nodules These nodules represent one of the pathognomonic features of rheumatic fever and have been reported to occur in 5 to 20 per cent of cases [47] In the recent cooperative study [1] of 500 cases of acute rheumatic fever they were observed in 21 7 per cent of the cases in the United Kingdom and in 7 4 per cent of the cases in North America While they may appear in connection with any other rheumatic symptoms their seriousness lies in their association with severe cardiac lesions which arise sooner or later in most cases Cheadle[15] assigned them an ominous prognosis because he observed that there was frequently a fatal pericarditis However I have repeatedly seen children with rheumatic fever and nodules recover and experience a favorable clinical course It is important to recognize these nodules because in some of the attacks they may represent the only local manifestation of rheumatic involvement as in the following case I observed

> A three year old child had a temperature between 99 5 and 100 5 F and was found to have subcutaneous nodules A diagnosis of rheumatic fever was made from this alone The diagnosis was confirmed six months later when while the patient was suffering from pallor loss of appetite and loss of weight the nodules reappeared but without fever or leukocytosis Examination revealed a large heart and signs of mitral stenosis pleural and pericardial effusions Four years later the nodules recurred in association with polyarthritis erythema annulare and urticaria Post mortem there was active rheumatic heart disease mitral stenosis cardiac hypertrophy and adherent pericardium

The nodules are grayish translucent conical or rounded elevations of circular or oval outline varying in size from that of a pinhead to about 2 cm in diameter They are situated subcutaneously unattached to skin so that the skin can be moved freely over the nodule They tend to occur over bony prominences and may be attached to fascia aponeuroses (especially the galea aponeurotica) tendons and periosteum (skull) The back of the elbow the bony prominences on the dorsum of the hand or foot the malleoli patella skull spines of scapula and of vertebrae are favorite sites of localization but the clavicles, ribs crests of the ilia sternum acromium and rarely the flexor tendons of the hand may also be involved They tend to assume a symmetrical distribution They vary in number from a few to over one hundred at a time As with other rheumatic symptoms there is frequently a characteristically rapid evolution and disappearance of nodules followed by recurrence in new locations Because of their occasional evanescence they may be overlooked Usually however, because of recurrences nodules may be observed for weeks or months There is no redness and usually no pain or tenderness (The pathology of subcutaneous nodules is discussed on p 820)

Cutaneous Lesions. The most significant cutaneous lesion is the lesion variously termed *erythema annulare* e marginatum e circinatum or e gyratum according to its configuration [42 47 46] I believe that this lesion is specific for rheumatic fever and is similar in importance to the subcutaneous nodule as a clue to the presence of the disease, the probability of cardiac involvement and the persistence of rheumatic activity A characteristic histologic picture has been described [14] As Cheadle[15] pointed out erythema annulare and subcutaneous nodules are often present simultaneously Coburn[16] found the former in 17 per cent of his series of cases a frequency which was slightly higher than that of the subcutaneous nodules In the recent cooperative study [1] of acute rheumatic fever, *erythema marginatum was observed in about* 4 per cent of the American cases and about 8 per cent of those in the United Kingdom

Characteristically the erythematous lesions occur on the trunk but may appear on the extremities They begin as reddish or violaceous macules or papules 1 to 5 mm in diameter (erythema papulosum) at which stage they are non specific They develop rapidly, literally under one s eyes into much larger lesions which by clearing in the center, form circles or segments of circles which join or intersect to trace various types of scalloped serpentine or crescentic patterns At their margins the lesions are pale pink or dull red

sharply circumscribed and slightly elevated, the centers are flat and colored by a faint brown pigmentation The lesions disappear almost as rapidly as they develop, only to reappear in new crops

The rheumatic significance of various other cutaneous lesions encountered is questionable *Urticaria* is of course not specific, but I have observed it developing in definite relation to attacks of rheumatic fever Various other erythemas reported in association with arthritis are not examples of rheumatic fever but belong to the group described by Osler[62] as erythema with visceral lesions *Erythema multiforme* except in so far as it may include erythema annulare is not related specifically to rheumatic fever and its appearance is coincidental Diffuse *petechiae* (very rarely white centered) are occasionally observed, but widespread purpura is not a feature of the disease[4] Most cases of purpura with arthritis or arthralgias are instances of Schonlein's disease (peliosis rheumatica) and are mistakenly called rheumatic fever *Erythema nodosum* sometimes reported as appearing in rheumatic fever is I believe a non specific toxic or allergic manifestation The painful *ephemeral nodules* described in the French literature probably represent the so-called Osler nodes in subacute bacterial endocarditis (p 872)

Chorea and Other Neurologic Symptoms The essentially rheumatic nature of chorea minor (Sydenham) is no longer questionable Hughes and Brown[42] who early emphasized its relationship to polyarthritis and endocarditis found evidence of rheumatic affection in 85 per cent of their cases of chorea Like the subcutaneous nodules with which it is frequently associated, chorea is essentially a manifestation of rheumatic fever in childhood In young male adults in the army in World War II, chorea was observed very rarely in association with rheumatic fever

It may be the first symptom and is frequently complicated or followed by carditis Among 1181 rheumatic children studied by Kaiser[45] chorea was the original expression of the disease in 326 or 28 per cent Carditis was associated or developed subsequently in 58 per cent Coombs[20] observed carditis in 76 per cent of cases and Osler[63] reported the cardiac valves intact in only 8 per cent of 125 fatal cases of chorea Chorea occurs preponderantly among females In pregnancy it is occasionally observed in a severe form (chorea gravidarum)[64], artificial abortion or premature induction of labor may be required

There has been some question as to the occurrence of a non rheumatic, possibly psychogenic chorea According to Coburn[17] and Kagan and Mirman,[43] at least one half of their observed cases of chorea in children were unaccompanied by other symptoms of rheumatic fever or by the development of cardiac disease These non rheumatic cases were characterized by absence of family history of rheumatic fever, absence of preceding respiratory infection and by normal leukocyte count and sedimentation rate during the attack of chorea

Clinically, chorea is characterized by constant, uncoordinated purposeless muscular movements Its onset is usually insidious but occasionally it develops immediately after a fall a trauma sudden fright or emotional upset In those cases commencing gradually the child begins to drop things, spill food and find it impossible to button her clothes She develops nervous symptoms including irritability, restlessness, sleeplessness night shrieks and bed wetting The child may be scolded at school for writing badly or slopping ink Exaggerated uncoordinated and explosive movements occur spontaneously as well as with muscular effort and are beyond voluntary control Facial grimaces rolling of the eyes, tossing of the head and wrinkling of the forehead combine to sketch a distorted picture The imbecilic appearance which results is belied by the school record of these children who are often unusually bright and even precocious Because of the disease however they slur their words phonate badly or may be unable even to speak They walk improperly, trip themselves move about irregularly and too rapidly in a manner which the title St Vitus' dance, well characterizes

In severe cases the children must often be kept in a bed with side bars in order to avoid self harm In such cases also they may be unable to swallow, requiring tube feeding as well as special nursing care because of loss of control of bladder and bowels Severe cases are easily recognized In mild ones there may be only a muscular restlessness The nature of the disease can be verified by requesting the child to hold her hands steadily outstretched for several minutes or by holding her hands enclosed in those of the examiner, whereupon the exaggerated twitchings are observed or

felt Chorea may occasionally affect a single extremity or half the body producing a picture simulating a monoplegia or a hemiplegia

A moderate leukocytosis and mild fever may be present but in the absence of other rheumatic manifestations the course is entirely afebrile Eosinophilia may be present The attack of chorea may last six to eight weeks or be even more protracted Recurrences are encountered sometimes with additional cardiac damage Death in an acute attack occurs in about 3 per cent of the cases, or in as many as 7 to 20 per cent when chorea occurs during pregnancy

Pathologically chorea is a meningoencephalitis involving particularly the basal ganglia especially the caudate nucleus and putamen in the corpus striatum and also the internal capsule and cortex[31] However the pathologic changes are usually surprisingly mild The almost invariable complete clinical recovery suggests that the alterations are essentially reversible and therefore are probably predominantly exudative Vascular lesions minute areas of softening degeneration of nerve cells and inflammatory foci have been described

Cerebral rheumatism was a term formerly applied to psychic disturbances including personality changes headache insomnia delirium and eventual coma associated with hyperpyrexia These manifestations are rare since the use of salicylates although toxic doses of the latter may also produce delirium and other mental disturbances More recently the finding of a chronic obliterating endarteritis (p 820) in the brains of persons dying of rheumatic heart disease has led to the concept that various clinical forms of rheumatic brain disease are due to these underlying lesions[1, 96] Rheumatic endarteritis of the brain has been found in 5 per cent of patients in a mental hospital and in 9 per cent of patients with dementia praecox Convulsive seizures (rheumatic epilepsy) have also been attributed to rheumatic cerebral lesions These interesting concepts are still hypothetical

Respiratory Symptoms Pharyngitis tonsillitis sinusitis and laryngitis occur frequently before the onset of an acute episode of rheumatic fever A specific rheumatic nature has sometimes been ascribed to these upper respiratory infections The characteristic rheumatic inflammation including Aschoff bodies has been observed in the peritonsillar fibrous tissue and adjacent musculatures Hoarseness and respiratory distress may be due to pressure on the recurrent laryngeal nerve inflammation of the crico arytenoid joints or large lymph nodes

Pleurisy either fibrinous or with effusion is observed clinically in 5 to 15 per cent and post mortem in more than 50 per cent of cases[65] Pleurisy is generally associated with pulmonary and cardiac disease including pericarditis[76] Pleural effusion may be unilateral or bilateral and occurs more frequently on the left side probably due to the proximity of the left pleura to the pericardium Paul[65] however found it more often on the right side at postmortem examination and even in the absence of gross pericarditis Microscopic lesions may have been present in the pericardium in such cases As indicated by Bezançon and Weil[8] the pleural lesions may arise by extension from cortical pulmonary disease (cortico pleurite) as well as from the pericardium

The onset of pleurisy is associated with sharp pain over the chest and intensified by inspiration or motion of the chest wall Pain may radiate to the abdomen and produce a picture resembling an acute abdominal complication A pleural friction rub may be present or only diminished breath sounds and a few subcrepitant rales After a few days the pain usually disappears and there are evidences of fluid at the bases of the lungs posteriorly The physical signs are often confusing because of the frequent association of pulmonary lesions and pericardial effusion The pleural effusion is rarely of sufficient size to produce significant respiratory distress or require tapping If routine anteroposterior and oblique roentgenologic views of the chest are taken a rheumatic pleurisy may be demonstrated in a high percentage of cases[87] The interlobar fissures appear thickened

The specific rheumatic nature of the pleurisy was first mentioned by Stoll and accepted by numerous French and English observers[65] Clinically a resemblance to rheumatic arthritis has been seen in the rapid development and subsidence of the pleurisy

Pathologically the rheumatic nature of the pleurisy has been supported by the observation of inflammatory lesions in the subendothelial connective tissue consisting of collagen swelling and degeneration edema infiltration

with lymphocytes, leukocytes and giant cells and scar formation, but Aschoff bodies have not been described

The pleural exudate[7] is serofibrinous appears turbid and straw colored and on standing one hour separates out a clear serous fluid and a coagulum containing a variety of cells French authors lay special stress on the characteristic nature of the cellular exudate which is composed of a predominance of polymorphonuclear leukocytes over lymphocytes and especially of endothelial cells occurring in large numbers both singly and in sheets The effusion is an exudate It may be hemorrhagic In many of the cases with sanguineous effusion, it is probable that the pleural exudate appeared in connection with pulmonary infarction Rapid and complete resorption of the effusion is the rule, but occasionally resorption is delayed (pleurésie fixé) and adhesions may develop

Pneumonia in Rheumatic Fever The occurrence of a *specific rheumatic* pneumonia has been the subject of considerable confusion and disagreement (p 820) Latham[51] and Fuller[3] first emphasized the occurrence of a rheumatic pneumonia physical signs of which they observed clinically in about 15 per cent of their cases of rheumatic fever Griffith et al[3] reported the clinical observation of pneumonitis in 11 3 per cent of 1046 patients with prolonged rheumatic fever The pathologic findings in the lung have been described above (p 820)

The reported clinical features of "rheumatic pneumonia" are even less consistent than the pathologic findings Rabinowitz[71] emphasized the presence of atypical bilateral, migrating signs of consolidation without the usual symptoms of pneumonia, i e, cough was slight or absent sputum scanty and fever of low grade Seldin and his associates[85] on the other hand characterized rheumatic pneumonia by the abrupt onset of profound breathlessness and orthopnea, hacking cough, scanty sputum which is occasionally blood streaked pleuritic pain and frequent cyanosis These symptoms are associated with high fever, leukocytosis and bilateral multilobar, nonsegmental infiltrations similar to the shadows of pulmonary edema Physical signs are relatively few According to Griffith and associates[3] rheumatic pneumonia is characterized by dyspnea and tachycardia fever pleuritic pain cough and malaise, shifting areas of dullness, diminished breath sounds and fine râles and transient pleural effusions The roentgen ray appearance is similar to that of primary atypical pneumonia

Lustok and Kuzma[88] found that fever dyspnea and tachypnea were almost always present, cough chest pain and cyanosis were very frequent and hemoptysis occurred in one third of the cases They stated that a clinical diagnosis of rheumatic pneumonitis was warranted on the basis of (1) disproportionate respiratory distress with severe cough chest pain, cyanosis and hemoptysis not relieved by oxygen, (2) evidence of carditis not severe enough to explain the pulmonary findings, and (3) roentgenologic finding of "increased perivascular markings arising at the hilus and progressing to nodulation, confluence and massive consolidation with relatively clear apices and bases"

It is very probable that the reported symptoms, physical and roentgen ray signs associated with so-called rheumatic pneumonia do not have a unitary pathologic basis, but result from pulmonary infarction left sided heart failure with or without transient pulmonary edema, as well as an atypical pneumonia which may or may not be characteristic of rheumatic fever In particular the occurrence of pulmonary infarcts, due to emboli from thrombi in the leg veins or right atrium, is often overlooked They may be characterized by sudden dyspnea, tachycardia, fever and leukocytosis with or without pleural effusion while the better known chest pain and hemoptysis are absent or over shadowed Heart failure may be precipitated or intensified by such emboli and, in particular, transient pulmonary edema may ensue Persistent rheumatic activity or recrudescence is often diagnosed when unrecognized pulmonary infarction occurs

Corresponding to these mixed pathologic lesions roentgenologic examination of the lung may disclose a variety of pictures[84] including (1) pulmonary congestion with increased vascular markings due to early left heart failure, (2) acute pulmonary edema with central densities radiating from the hilar regions (3) pulmonary infarcts often indistinguishable from areas of consolidation or atelectasis (4) pleural effusion which may be due to rheumatic inflammation or to pulmonary infarction, (5) "rheumatic pneumonitis" characterized by large, small or

confluent densities indistinguishable from atypical pneumonia, atelectasis or infarction In cases of prolonged rheumatic fever and rheumatic heart disease there may be roentgen ray evidence of chronic pulmonary edema pulmonary fibrosis and pleural thickening

Gastrointestinal and Abdominal Symptoms Constipation diarrhea and abdominal distention have been noted as frequent complaints in children prior to development of definite rheumatic fever ('pre-rheumatic children')

Abdominal pain is a common and serious symptom There may be abdominal tenderness nausea and vomiting I have occasionally observed such patients mistakenly operated upon for acute appendicitis Abdominal pain may arise by several mechanisms Most commonly it is referred from the chest, where there is a pericarditis or pleurisy There may be a polyserositis including a perihepatitis as well as pleuropericarditis In right sided heart failure, pain abdominal tenderness and vomiting may be due to a congested liver I have reported two cases in which an appendectomy was performed because of abdominal pain and tenderness due to a diffuse necrotizing arteritis involving the appendiceal as well as other vessels[4] Pain may result from a serous peritonitis Rhea[73] recently observed such a case in which he reported finding a rheumatic inflammation but his microphotographs do not appear to show specific lesions

Renal Symptoms Intermittent slight *albuminuria is common in the presence of fever* According to Goldring and Wyckoff[29] there is often a mild focal nephritis as indicated by abnormal urinary protein casts leukocytes and erythrocytes determined by the Addis sediment count

Acute diffuse glomerulonephritis is uncommon, occurring in less than 1 per cent of cases of rheumatic fever[76] Baehr and Schiffrin[4] discovered only 2 cases of acute diffuse glomerulonephritis among 235 necropsied cases of rheumatic heart disease Glomerulonephritis and rheumatic fever were found by Hartman and Bland[38] to be associated in 2 5 per cent of 117 cases of clinically diagnosed acute nephritis

Diseases of Blood Vessels The diffuse vascular lesions described by Klotz[50] and by von Glahn and Pappenheimer[85] are clinically insignificant I have reported with Gross[24] four anatomically proven cases of active rheumatic heart disease with diffuse necrotizing arteritis In these cases the vascular lesions were sufficiently extensive to produce symptoms which dominated the clinical picture including orchitis and abdominal pain which induced surgical intervention

Epistaxis has been repeatedly noted as a manifestation of rheumatic children, especially during rheumatic activity or before a recurrence[illegible] I believe the frequency and significance of epistaxis as a specific rheumatic symptom has been exaggerated

Blood and Urine A *leukocytosis* is common in active rheumatic fever[89] and is a significant index of active infection The white blood count is generally between 10 000 and 16 000 per cubic millimeter Occasionally it may exceed 20 000 or it may lie within normal limits Salicylate and hormone therapy may lower the white blood count as well as the temperature A leukocytosis may persist into the afebrile stage It then becomes a more delicate index of rheumatic activity than the temperature An absolute and relative increase in polymorphonuclear leukocytes accounts for the leukocytosis There is a shift to the left in the number of non filamented polymorphs by the Schilling count The remaining white cells are normal but in chorea there may be an eosinophilia[5]

Anemia is a common feature of active rheumatic fever The hemoglobin may fall as low as 6 or 7 gm per 100 cc although it usually lies between [illegible] and 12 gm and *gradually rises as rheumatic activity subsides* The red blood cell count ranges between 3 and 4 million per cubic millimeter The anemia is of the microcytic type[illegible]

That the *rate of sedimentation of red blood cells is increased* in rheumatic fever was observed by *Kahlmeter*[44] In one hour the column of plasma by Westergren's method may reach 100 to 120 mm as compared with 1 to 7 mm for normal women and 1 to 11 mm for men With subsidence of rheumatic activity the rate of sedimentation reverts to normal Of great significance however is the observation that the sedimentation rate may remain rapid for some time after the temperature and white count become normal[illegible] Thus it appears to be an especially sensitive index of persistent rheumatic infection With congestive heart failure occasionally the sedimentation rate may fall to normal even in the presence of rheumatic activity[66] but see

p 156 In cases of chorea without associated manifestations of rheumatic fever or carditis, the sedimentation time is normal[17]

The *C reactive protein*[94] not present in normal blood, appears in the blood (probably in the beta globulin fraction[100]) in a variety of infections and other conditions including acute rheumatic fever[2, 74] It is absent in inactive rheumatic fever This protein reacts in vitro with the somatic "C" polysaccharide of pneumococci to give a precipitate A positive reaction is graded from 1 plus to 8 plus In general the presence of C reactive protein in the serum during rheumatic fever tends to parallel the erythrocyte sedimentation rate, but some observers regard it as a more sensitive index of rheumatic activity However, because of its non specificity it is not diagnostic of rheumatic fever Its value rather is to determine activity in a patient known to have rheumatic fever but no other disease associated with C-reactive protein It may also be helpful in excluding active rheumatic fever in a doubtful case, if no C reactive protein is present

The *fibrinogen* content of the blood plasma was reported as being elevated by Bezançon and Weil,[8] who use this as a sign of persistent activity It appears to parallel the sedimentation rate

An *abnormal (shortened) coagulation band in the Weltmann reaction* is associated with rheumatic activity and was considered by Scherlis and Levy[11] to be at least as significant in this respect as the rapid sedimentation rate

The *formol-gel* test may be positive, but this is only irregularly found with active rheumatic fever The positive formol gel test corresponds with the tendency to high serum globulin in rheumatic fever[22, 62]

Serum mucoprotein was found to be elevated during the active disease,[49] and the concentration returned to normal more slowly than the erythrocyte sedimentation rate Hence it was suggested that serum mucoprotein may be a more sensitive index of persistent rheumatic activity An elevated serum mucoprotein is also found in a variety of other conditions Similarly *serum hexosamines* which are constituents of serum mucoprotein, are also elevated in almost all patients with rheumatic fever at some time in the course of the disease[77, 45] But the elevation in serum hexosamine is not necessarily the cause of the increased serum mucoprotein in rheumatic fever The elevation in serum mucoprotein and serum polysaccharide has been related to the concept that rheumatic fever is a disease of mesenchymal tissue particularly of the interstitial ground substance The latter is rich in mucopolysaccharides, especially in hyaluronic acid Hexosamines (glucosamines) arise as a result of the depolymerization of hyaluronic acid by hyaluronidase

Hyaluronidase inhibitor (antihyaluronidase) is present in the serum in increased concentration during active rheumatic fever[30]

Diphenylamine Reactor[18] The blood contains an unidentified substance which reacts to diphenylamine and is increased in concentration during the peak or shortly after the height of acute rheumatic fever but occurs also in other conditions

Blood cultures are generally negative In about 5 per cent of cases an occasional positive *blood culture is obtained usually of the* Streptococcus viridans (alpha) or anhemolyticus (gamma)[55] But these organisms are almost invariably grown only in fluid media a point which indicates that the organisms are few in number On the other hand positive cultures of these organisms in subacute bacterial endocarditis are obtained as a rule both on solid and fluid media

The *urine* contains a trace of *albumin* in the febrile state and in the presence of congestive heart failure

ELECTROCARDIOGRAPHIC CHANGES

Electrocardiographic abnormalities are almost always present at some time during the course of active rheumatic fever[11, 40] These disturbances are only occasionally recognizable clinically Since the arrhythmias are characteristically evanescent, the frequency with which they are discovered is proportional to the frequency of cardiac and electrocardiographic examination

The importance of electrocardiographic changes in rheumatic fever lies in the facts that (1) they suggest the occurrence of cardiac damage in almost every case of that disease, (2) they may serve as an important sometimes as the only, sign of cardiac damage Shapiro[84] demonstrated the persistence of active disease in 65 per cent of children with supposedly quiescent rheumatic heart disease by taking successive electrocardiograms which revealed abnormal or changing curves There is a mistaken notion that these

electrocardiographic changes are themselves diagnostic of rheumatic carditis On the contrary, the changes are nonspecific and are confirmatory only if the diagnosis of rheumatic fever is justifiable on other clinical grounds Similar changes are found in a host of infections and other conditions in which chronic clinical heart disease does not develop

Three types of electrocardiographic abnormalities are encountered in rheumatic fever (1) impaired atrioventricular conduction (2) abnormalities in the QRST complex and more rarely in the P wave and (3) changes in cardiac rate and rhythm

1 Impaired Atrioventricular Conduction

(a) *Prolongation of the P R interval* is the most frequent significant electrocardiographic abnormality in rheumatic fever The P R interval exceeds 0 20 second occasionally lies between 0 3 and 0 4 and even longer P R intervals have been observed Prolonged P R interval has been noted in 25 to [illegible] per cent of active cases the higher incidence being obtained with frequent and numerous electrocardiographic examinations[illegible, 80, 61] A prolonged P R interval may be encountered in a great variety of infections and infectious diseases (Chapter 36) but not as regularly as in rheumatic fever As a rule the prolongation of the P R interval is a transient disturbance but occasionally it persists for weeks or months

The prolongation of the P R interval may be due directly to reversible rheumatic inflammation of the a v node and bundle[83] but it has also been attributed to vagal stimulation[illegible] Thus carotid sinus pressure and prostigmine may increase the prolongation of the P R interval[illegible] while atropine reduces the P R interval in rheumatic fever[75] These observations however, do not exclude the possibility that the effect of rheumatic fever is on the conduction system directly, while the augmenting or inhibitory effect of the drugs is by way of the vagus nerve Furthermore rheumatic lesions may render the a v conduction system abnormally sensitive to vagal stimulation

(b) More severe grades of *heart block* are occasionally observed with 2 1 3 1 or 3 2 block Dropped beats and Wenckebach periods have been noted Complete heart block is very uncommon but it may be the earliest manifestation of rheumatic heart disease and may occur in the absence of fever[93, 97] Rarely there is an Adams-Stokes syndrome[illegible] Almost always heart block disappears when the infection subsides but occasionally it persists permanently Bundle branch block is observed occasionally Interference dissociation (p 330) may be an early finding and occurred in 18 of 1000 cases of rheumatic fever studied by Rosenberg[78]

2 Abnormalities in QRST and in P Waves

The frequency of QRS ST and T wave changes in rheumatic fever was emphasized by Cohn and Swift[19] and by Rothschild et al[78] Blackman and Hamilton[9] reported finding ST and T wave changes in 61 per cent of their cases

(a) *Deviations in R T or S T interval* There may be an elevation or depression of RST transition Most often there is an R T elevation in two or more leads due to rheumatic pericarditis

(b) *T wave alterations* consist of inversion especially in leads I and II Similar T wave inversions and R T abnormalities are observed also or only in the precordial leads[3, 22] The T waves may also be diphasic or of low voltage Inverted T waves in some cases are due to pericarditis with effusion

(c) Changes in the QRS complex consist of lowering of the voltage of the major deflection or occasionally of notching slurring and widening due to delayed intraventricular conduction or bundle branch block

(d) A *prolongation of the Q T interval* relative to the cardiac cycle (corrected Q T interval or Q T) has been stressed as a universal finding in active rheumatic carditis by Taran and Szilagyi[81, 13] They found the Q T interval to be a measure of the severity of the carditis and valuable both for following progress and discovering persistent activity even when all other laboratory criteria are normal A confirmatory study was reported by Kornel and Braun[50] The value of measuring the Q T interval and its clinical significance are still moot questions Technical difficulties in measurement impair any practical value

(e) P wave inversion or flattening has been described as evidence of rheumatic activity[81]

3 Changes in Cardiac Rate or Rhythm

(a) *Sinus tachycardia* is almost always found in the presence of fever and often for a variable period after the fever is gone Occasionally there are attacks of paroxysmal tachycardia Bradycardia is rarely found in

Chapter 33

RHEUMATIC FEVER

Diagnosis, Differential Diagnosis, Prognosis and Treatment

DIAGNOSIS OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

The diagnosis of rheumatic fever and rheumatic heart disease[5, 41] involves the recognition of (1) active rheumatic fever with or without cardiac involvement and (2) rheumatic heart disease in patients without rheumatic activity.

THE PRESENCE OF ACTIVE RHEUMATIC DISEASE

It is important to reemphasize that there is no specific test for rheumatic fever and that diagnosis of this disease is often necessarily based on non specific clinical and laboratory abnormalities which are similar to those caused by other diseases. In order to establish relatively uniform statistical data and to avoid the serious implications, restrictions and psychologic disturbances that accompany a diagnosis of rheumatic fever, it seems desirable to satisfy strict criteria before this diagnosis is justified. The frequent discovery of rheumatic heart disease on physical or postmortem examination in subjects who presented no history of rheumatic fever suggests that the latter is often overlooked or that it often occurs in a subclinical unrecognizable form. However, this does not justify the overemphasis in recent years on minor and nonspecific abnormalities as an adequate basis for the diagnosis of rheumatic fever.

Rheumatic fever may be indicated by cardiac or extracardiac symptoms. Even when there are only extracardiac symptoms the probability of cardiac involvement in the first or subsequent attacks of rheumatic fever is so great that the patient must immediately be considered as having actual, possible or potential heart disease. The diagnosis of rheumatic fever is relatively simple when several of the more characteristic features develop simultaneously or in rapid sequence. Difficulty arises when there are only non specific *general* symptoms such as fever, tachycardia, etc., or when there is only a single localizing symptom such as joint pains.

Criteria for Diagnosis of Active Rheumatic Fever

The diagnosis of rheumatic fever is often based on certain "major" and "minor" criteria as set up by Jones.[55] With slight modification, the major criteria include (1) carditis, (2) arthritis or arthralgia, (3) chorea, (4) subcutaneous nodules and (5) erythema annulare (marginatum).[36, 76] Because of the relative infrequency of the last three the major diagnostic criteria are usually carditis and arthritis. According to Jones[55] a diagnosis of rheumatic fever is justified in a given case if two major manifestations are present. This is generally satisfactory since usually one of these is carditis. But it is essential that the evidence for carditis be acceptable (infra).

According to Jones also a diagnosis of rheumatic fever is generally justified if there are one major and two minor manifestations. This is satisfactory if the major manifestation is carditis, subcutaneous nodules or erythema annulare, and possibly chorea, and if one is certain of the accurate interpretation of these symptoms. But this combination of criteria is frequently inadequate for the diagnosis of rheumatic fever if the major manifestation is arthritis, since it is often impossible to differentiate rheumatic from other forms of arthritis. Thus the combination of arthritis or arthralgia, fever and a rapid sedimentation rate is commonly used as a basis for the diagnosis of rheumatic fever. Yet the joint symptoms may actually be due to rheumatoid arthritis, Still's disease, lupus erythematosus

osteomyelitis, leukemia, sickle cell anemia, undulant fever or other conditions and the fever and rapid sedimentation rate are common to all of these.

The *minor criteria* or manifestations of rheumatic fever may be classified into two groups. The first includes malnutrition, pallor, fatigability, recurrent sore throat, frequent epistaxis, abdominal pain, precordial pain and pulmonary findings. These serve at most to arouse suspicion when they occur in a child or adolescent and to stimulate careful observation for possible rheumatic fever. The second group includes fever, leukocytosis, increased rate of erythrocyte sedimentation, presence of C reactive protein or a high titer of antistreptolysin, antistreptokinase or hyaluronidase inhibitor. These are non specific findings which are not diagnostic of rheumatic fever but denote rheumatic activity, *provided a diagnosis of rheumatic fever can be otherwise supported on the basis of the major manifestations.* On the other hand, absence of fever, leukocytosis, rapid sedimentation rate, etc., except during treatment with large doses of salicylates or adrenal cortical drugs, would almost always exclude the diagnosis of rheumatic fever (but not chorea). In the child with definite evidence of rheumatic cardiovalvular disease, especially with a recent previous attack of rheumatic fever, the diagnosis of a rheumatic recurrence should be entertained on less rigid criteria than are required to diagnose the first attack. Similar latitude may be considered during epidemics of definite rheumatic fever, e.g., in boarding schools or barracks.

Arthritis and Arthralgias. In evaluating the presence of arthralgias or arthritis a distinction should be made between muscle and tendon "growing pains," which are non rheumatic, and definite joint pains, which may or may not denote rheumatic fever.[98] A striking, rapid amelioration of pain and fever should follow adequate doses of salicylates, but this response in itself cannot be accepted as sufficient evidence for the diagnosis of rheumatic fever. A streptococcal sore throat or scarlet fever one to three weeks preceding the arthritis enhances the probability of rheumatic fever but is likewise not an absolute diagnostic criterion.

Carditis. The most important feature of rheumatic fever and the most definitely diagnostic is cardiac involvement. *The combination of fever with congestive heart failure, rapidly progressive cardiac enlargement or pericarditis* in a child or young adult almost always denotes active rheumatic fever. Evidence of endocardial or valvular involvement, as indicated by cardiac murmurs, is sometimes difficult to evaluate in the presence of fever and anemia. In a child with previous rheumatic cardiovalvular disease, the occurrence of new murmurs, fever or arthritis is strongly indicative of another attack. In the adult over 25 years of age this is less certain (p. 843). In the child with fever, the recent appearance of apical and pulmonic systolic murmurs in combination with rapid, tumultuous cardiac action is indicative of rheumatic carditis. This is even more probable if there is an apical presystolic or mid diastolic murmur or a triple rhythm due to a loud third sound or gallop rhythm. In the young adult, benign non specific pericarditis (p. 603) is difficult to exclude if there is no evidence of valvular heart disease or heart failure. As a rule careful observation will disclose confirmatory findings such as arthritis, subcutaneous nodules or distinctive erythemas in the child with rheumatic fever and pericarditis.

Electrocardiographic abnormalities, especially a pronounced prolongation of the P R interval, are in themselves or in combination with fever insufficient to justify a diagnosis of rheumatic fever or rheumatic heart disease, since these abnormalities occur with many other infections and infectious diseases (Chapter 36). However, they may indicate cardiac involvement or continued activity in cases in which the diagnosis of rheumatic fever or rheumatic heart disease is justified on other grounds. Polyfocal extrasystoles, ectopic tachycardias including atrial fibrillation and sinoatrial, atrioventricular and bundle branch block are other electrocardiographic abnormalities which may indicate cardiac involvement in a patient with rheumatic fever.

Sydenham's chorea is suggestive of rheumatic fever even when it occurs as an isolated symptom. But when it occurs in association with fever, arthritis or other symptoms of rheumatic fever which in themselves are non specific, a definite diagnosis of rheumatic fever is justified.

Subcutaneous nodules and *erythema marginatum (annulare)* are in themselves diagnostic of rheumatic fever, but there are occasional errors in interpretation of these

subcutaneous and cutaneous lesions As a rule *the diagnosis can be made with certainty* because careful observation will disclose simultaneous fever, joint pains, carditis or other rheumatic phenomena

Laboratory Aids in the Diagnosis of Rheumatic Fever[71,172]

There is no specific laboratory test that is analogous to the Wassermann test for syphilis The presence of streptococcus A antibodies in high titer in the serum, especially antistreptolysin O is indicative of recent Streptococcus hemolyticus infection and indirectly of rheumatic fever if there are clinical manifestations of the latter The antistreptolysin O titer in rheumatic fever usually exceeds 250 units (p 809) but is more significant when it exceeds 400 or 500 units [86,14,92] Serial determinations are preferable since an increased antibody titer usually becomes detectable only the second week after the streptococcal infection and does not attain maximal levels for four to six weeks When rheumatic fever is doubtful clinically, a persistently normal antistreptolysin titer tends to exclude that diagnosis Occasionally the titer of antifibrinolysin (antistreptokinase) or hyaluronidase inhibitor is high in rheumatic fever when that of antistreptolysin is not Since either the antistreptolysin O, antistreptokinase or hyaluronidase inhibitor concentration is significantly elevated in 95 per cent of cases of acute rheumatic fever normal values for all three strongly oppose a diagnosis of rheumatic fever All other laboratory findings in rheumatic fever (p 835) are non specific and not diagnostic Many of them are useful however to determine the persistence of activity in a known case of rheumatic fever

Signs of Persistent Rheumatic Activity

When typical clinical signs of rheumatic fever disappear persistent rheumatic activity may be denoted by various clinical or laboratory findings These include

Fever A low grade fever may persist for many weeks or months This may be discovered only by rectal thermometry performed several times daily On the other hand good clinical judgment often justifies disregarding prolonged low grade elevations in temperature in the absence of other significant manifestations Some normal children have a temperature slightly beyond the usual normal range [110] Disappearance of fever *is suggestive of subsidence of activity provided* that salicylates or similar antirheumatic drugs have been discontinued On the other hand, it is generally well known that rheumatic activity often persists for weeks after the temperature has fallen to normal and that such rheumatic activity may be disclosed by other clinical or laboratory findings

Tachycardia A rapid cardiac and pulse rate persists as a rule, even after the temperature is normal It usually denotes rheumatic activity and often cardiac impairment However, occasionally a rapid pulse rate during convalescence slows if the patient is gradually permitted to resume activity In such instances the tachycardia is due to a generally poor physical fitness (lack of training) rather than to specific myocardial disease Not infrequently a persistent tachycardia is of "nervous" or psychic origin and the sleeping pulse rate is found to be normal [91]

Leukocytosis Although the white blood count may be normal, there is usually a leukocytosis in the presence of persistent rheumatic activity Special emphasis is placed on a polymorphonuclear shift to the left in the Schilling hemogram Often leukocytosis in acute rheumatic fever persists for days or weeks after the disappearance of fever

Increased Sedimentation Rate of Erythrocytes This is generally regarded as a sensitive test of persistent rheumatic inflammation Accuracy in performance of the test is essential if this is to be used as a decisive factor in determining the presence of persistent rheumatic activity Occasionally slight elevations in sedimentation rate (up to 40 mm in one hour) are found in individuals without apparent disease In rheumatic fever the sedimentation rate is usually between 60 and 130 mm in one hour but this may be depressed in the presence of heart failure

The presence of C reactive protein in the serum is a very sensitive index of rheumatic activity and has been used as a guide to therapy [2,101,87] The C-reactive protein may disappear and the sedimentation rate return to normal during adequate salicylate or adrenal cortical hormone therapy before the attack of rheumatic fever is over (p 853)

Persistent weight loss or failure to gain is associated with active rheumatic fever Subsidence of activity usually is followed by

restoration of appetite and progressive gain in weight. Increased weight due to edema of heart failure must be excluded.

Electrocardiographic Abnormalities. Distinct prolongation of the P-R interval and especially continued electrocardiographic changes in successive records are usually indicative of persistent rheumatic activity.

Clinical observations must be carefully evaluated in any determination of persistent rheumatic activity. There must be no evidence of carditis, arthritis or other manifestations of rheumatic fever and the general appearance and behavior of the patient should signify the absence of active disease. In children and young adults with rheumatic cardiovalvular disease, progressive cardiac enlargement or the development or persistence of heart failure usually denotes persistent rheumatic activity whether or not there are any of the above-mentioned clinical or laboratory signs. *The presence of minor rheumatic manifestations* should suggest persistence of activity, even though such minor phenomena would not be sufficient to diagnose the actual attack of rheumatic fever. In fact *it is important to emphasize that the clinical and laboratory phenomena which denote persistent rheumatic activity are to be distinguished from those manifestations which are originally diagnostic of the disease.*

In my experience many a child and young adult with unexplained low grade fever has been long invalided and unfairly tagged with the diagnosis of rheumatic *fever* when the sedimentation time was found to be rapid—as if the unexplained fever suggested and the rapid sedimentation rate confirmed the diagnosis. A functional systolic murmur added to these two features frequently completes the unfortunate triad which leads to the unwarranted sentence of rheumatic heart disease. Not infrequently, determination of the temperature after the child has been at complete rest for half an hour dissipates the "fever," determination of the sedimentation rate by an expert slows the rate of fall of the erythrocytes to normal, and listening to the heart in full inspiration eliminates the murmur.

Cardiac Involvement During Acute Rheumatic Fever

Every attack of rheumatic fever involves the concomitant diagnosis of potential or possible rheumatic heart disease. A definite diagnosis of rheumatic heart disease during the attack must be based on symptoms and signs of cardiac failure, pericarditis or definite cardiac enlargement under observation. Diastolic gallop rhythm, a diastolic murmur, distinct prolongation of the P-R interval in the electrocardiogram, disproportionate and protracted tachycardia are suggestive but not definite evidences of organic rheumatic cardiac disease. A *loud* systolic murmur with radiation to the axilla, which is constant despite exercise or changes in position or respiratory phase and which persists for more than six months after subsidence of the acute attack, also denotes organic heart disease. However, the variability and regression of physical signs in organic rheumatic heart disease in children have been stressed by several observers.[11, 127]

Rheumatic Fever in Adults

The entire problem of acute rheumatic fever in adults requires reevaluation. I have become more and more skeptical of the diagnosis of clinical active rheumatic fever in subjects beyond the age of 20, whether or not the patient has rheumatic cardiovalvular disease. The problem of active rheumatic fever in the adult arises chiefly under three sets of circumstances: (1) An adult with or without previous rheumatic valvular disease develops *polyarthritis* and usually fever and a rapid sedimentation rate. (2) An adult with rheumatic cardiovalvular disease develops *fever*. (3) An adult with rheumatic valvular disease who has been well compensated for years develops progressive *congestive heart failure* without apparent cause.

1. In the first circumstance, that of arthritis, the diagnosis almost always should be rheumatoid arthritis, infectious arthritis or some other disease associated with arthritis rather than rheumatic fever. Again we must emphasize that there is no specific diagnostic test for rheumatic fever. No matter what lists of diagnostic criteria we set up or what arithmetical value we give to each, the diagnosis of rheumatic fever is unproven clinically unless unequivocal rheumatic heart disease develops. Polyarthritis in adults may be attributed to rheumatic fever if it is associated with heart failure or pericarditis or if new organic murmurs develop and persist. Even then, exceptionally, the heart failure and pericarditis do not necessarily prove rheumatic fever. In my experience polyarthritis in adults is not followed by the development of mitral

stenosis or aortic insufficiency except in very rare instances Since rheumatic fever is important because of its eventual cardiac complications and since in children unequivocal rheumatic fever almost always causes rheumatic heart disease arthritis in adults which does not produce heart disease is best not termed rheumatic fever

This is closely related to the problem of rheumatic fever and rheumatoid arthritis Whatever the findings of pathologists, these *two are different clinical diseases* Rheumatic fever is important because of its almost invariable cardiovalvular damage It does not cause persistent or progressive deformity and disability of the extremities Rheumatoid arthritis is important because it frequently causes deformity and disability of the extremities, *clinically* it is extremely exceptional to observe the development of rheumatic heart disease with rheumatoid arthritis By these criteria the nonspecific forms of arthritis in adults are not instances of rheumatic fever but of rheumatoid arthritis

2 When a person with inactive rheumatic heart disease develops fever, there is a tendency to attribute it to rheumatic fever if there is no other apparent cause This is partly due to the established teaching that rheumatic fever is a continuing disease even throughout adult life as evidenced by the finding of Aschoff bodies in a high percentage of cases at autopsy[90] and more recently in biopsies of atrial appendages at operation (p 817) But it is becoming apparent that Aschoff bodies are not always evidence of active rheumatic fever in the clinical sense, since there is no good correlation between the presence or absence of Aschoff bodies and clinical evidence of rheumatic activity It may be that more detailed study of the life cycle of the Aschoff body and the histochemical attributes of different Aschoff bodies may distinguish those which are fresh or active from those which represent the healed stage (p 818)

In my experience the occurrence of unexplained persistent fever in the *adult* patient (beyond 25) with rheumatic heart disease is virtually never due to rheumatic fever but is usually due to bacterial endocarditis if there is no previously established heart failure In *adult* patients with rheumatic heart disease and previously established heart failure unexplained fever for more than a week or two is likewise not due to rheumatic activity, but to pulmonary emboli or patchy bronchopneumonia

3 Finally, the development of congestive heart failure without apparent precipitating cause in the previously compensated adult rheumatic cardiac, or the progression of congestive heart failure, is attributed to rheumatic activity in the heart although there are no other clinical manifestations of active rheumatic fever This likewise is based without systematic evidence of clinical pathologic correlation on the studies showing the frequency of Aschoff bodies in the hearts of adult rheumatic cardiac patients However, the more carefully the clinical history is taken or the more closely the patient is observed the more often the onset of heart failure will be found to be precipitated by a non rheumatic infection, by unusual physical activity, by excessive sodium intake, by pulmonary embolism by tachycardia, by the onset of atrial fibrillation or by associated hypertensive or coronary heart disease In many other cases the development or progression of heart failure is apparently due to the prolonged mechanical strain of a severe valvular lesion as indicated by localization of heart failure *retrograde to the chamber* under strain, and by the amelioration of heart failure by surgical relief of the valvular lesion That heart failure in the adult rheumatic cardiac, who has had a relatively long period of compensation after his childhood rheumatic fever, is frequently or to any large extent *due to recurrent* rheumatic activation is unproven *It is* even a harmful concept if used as a *basis of* treatment of the patient

THE PRESENCE OF RHEUMATIC HEART DISEASE *IN PATIENTS WITHOUT ACTIVE RHEUMATIC FEVER*

This is generally the problem encountered in adult patients who often appear *healthy* and are unaware of any cardiac disease The physician must determine whether or not there is organic heart disease, and if present whether such heart disease is of rheumatic etiology

The existence of cardiac disease is usually clear when there are definite symptoms of heart failure, or of pronounced cardiac enlargement In the absence of such symptoms and signs the diagnosis is dependent on physical and roentgen ray examination and

electrocardiography In rheumatic heart disease the diagnosis usually is based on recognition of the evidences of valvular heart disease (Chapters 26–29) These evidences include characteristic murmurs and distinctive forms of cardiac enlargement as visualized by roentgen ray

When the presence of organic heart disease has been determined its rheumatic etiology may be surmised if there is a definite history of rheumatic fever This assumption is especially probable if there is also a history of a cardiac murmur which persisted after the rheumatic attack However more than half of young adults with rheumatic heart disease present no history of rheumatic fever [64]

The character of the valvular lesion is often suggestive of the rheumatic etiology The combination of aortic insufficiency and mitral stenosis or mitral stenosis alone almost always denotes rheumatic cardiovalvular disease Aortic stenosis as a rule signifies rheumatic heart disease although occasionally it may represent a congenital aortic or subaortic stenosis or rarely it may be due to non rheumatic calcification Aortic insufficiency alone is usually rheumatic or syphilitic the differential diagnosis is discussed elsewhere (p 692) Organic systolic murmurs may represent rheumatic mitral valvular disease or aortic stenosis but must be differentiated from functional murmurs (p 647) and murmurs due to congenital cardiovascular lesions (p 794)

Sometimes a rheumatic mitral stenosis is first suggested by left atrial enlargement on fluoroscopic or roentgenographic examination by unexplained hemoptysis atrial fibrillation cerebral embolization or heart failure Similarly aortic insufficiency may be first suggested by the abnormal configuration of the heart or by abnormal circulatory dynamics associated with this lesion (p 690)

That the rheumatic heart disease which the physician has diagnosed is *inactive* depends on negative data particularly the exclusion of all of the symptoms presented under active rheumatic fever

DIFFERENTIAL DIAGNOSIS OF RHEUMATIC FEVER

Since the discovery of rheumatic heart disease often depends on the recognition of non cardiac evidences of rheumatic fever it is important to consider the differential diagnosis of the general disease as well as of the cardiac lesion Problems in the differential diagnosis of rheumatic fever arise when there are only general non specific symptoms of an obscure infection or when the local symptoms present are confined to a single organ system

1 *Subacute Bacterial Endocarditis* This offers one of the most frequent problems in differential diagnosis in adults with compensated rheumatic heart disease The patient is recognized as having rheumatic valvular heart disease, but the physician must decide whether the fever and other symptoms present are due to activation of a rheumatic infection or to a complicating subacute bacterial endocarditis or to both The differential diagnosis is discussed on pages 877–878

2 *Grippe ' nasopharyngitis or other infections of the respiratory tract* may be erroneously diagnosed as rheumatic fever or vice versa Following a mild upper respiratory infection in a child there may be persistent low grade fever and indefinite muscle or juxta articular pain These are insufficient to diagnose rheumatic fever even when the sedimentation rate is rapid However awareness of the possibility of rheumatic fever may lead to careful observation and eventual discovery of cardiac involvement, arthritis nodules or characteristic rheumatic dermatoses A so called grippe or pneumonia ' followed several months later by definite cardiovalvular disease may have to be reinterpreted as an attack of rheumatic fever

3 *Pulmonary tuberculosis* may be considered when the rheumatic child presents fever anorexia pallor and malnutrition Roentgenographic examination of the chest tuberculin tests and sputum examinations decide the problem I have several times observed a tuberculous arthritis in a child treated as rheumatic fever until expert roentgenologic examination of the joint suggested the correct diagnosis

4 *Rheumatoid Arthritis in Adults and Still s Disease in Children* Rheumatoid arthritis is distinguished essentially by the absence of cardiac involvement Electrocardiographic abnormalities which are the rule in rheumatic fever, are absent in rheumatoid arthritis In rheumatoid arthritis the small joints are more frequently and more severely affected They may assume a persistent fusiform or

spindle shaped appearance Deformity and ankylosis are common but may develop only in advanced stages The rapidly migrating character of the rheumatic polyarthritis is rarely observed in rheumatoid arthritis and salicylates do not produce as dramatic a relief of pain disappearance of swelling and effusion and restoration of normal temperature

Still s disease in children is differentiated by the presence of rheumatoid arthritis and by the association of diffuse adenopathy and splenomegaly

5 *Osteomyelitis* may simulate rheumatic fever because of pain near the end of an extremity and the presence of fever Careful localization of the pain and tenderness and later roentgenologic examination suggest the proper diagnosis

6 *Leukemia and Cooley s Anemia* I have seen cases of these diseases erroneously diagnosed as rheumatic fever because of the combination of joint pains, pallor and anemia, and a cardiac murmur Fever may also be present Roentgen ray examination discloses characteristic bony lesions and abnormal cells are found in the blood

7 *Sickle cell anemia* may likewise be characterized by joint pains, anemia abdominal pain and a cardiac murmur which may be diastolic Its differential diagnosis is discussed on page 1052

8 *Poliomyelitis* may be confused with rheumatic fever but meningeal signs spinal fluid abnormalities and paralyses characterize the former Pains in the muscles should be distinguished from the joint pains of rheumatic fever

9 *Schonlein's disease* (peliosis rheumatica) is characterized by joint pains but can be distinguished by extensive purpuric lesions near the joints and by the absence of cardiac or other features of rheumatic fever

10 *Scurvy* Pain and swelling may seem to be localized to the joints and may suggest rheumatic fever The disease occurs mostly during infancy at which time rheumatic fever is rare A history of dietary deficiency ecchymoses (especially at the lower end of the femur), swelling and sponginess of the gums, characteristic roentgen ray appearance of the bones and therapeutic response to vitamin C are features of scurvy

11 *Hemophilia* is associated with hemorrhage into the joints with consequent pain and swelling Blood clotting studies are necessary for diagnosis

12 *Congenital syphilis* may simulate rheumatic fever when there is pain and swelling near the joints due to epiphysitis A positive Wassermann test and distinctive roentgenologic findings in the bones are diagnostic By similar means it is possible to distinguish the rapidly developing usually painless joint swellings occurring in late congenital or acquired syphilis (Charcot joints)

13 *Disseminated lupus erythematosus* is often diagnosed as rheumatic fever because of the frequent combination of fever and arthralgias or arthritis at the onset and the occasional presence of a pericardial rub It is distinguished by the appearance of the characteristic butterfly rash on the face and bridge of the nose, by lesions on fingers and palms, by leukopenia and by L E cells in blood or marrow

14 *Gonococcemia and Gonorrheal Arthritis* The history of urethral discharge, the tendency to monarticular involvement and the absence of striking response to salicylates aid in distinguishing gonorrheal from rheumatic arthritis When gonococcemia occurs there may be chills and papulovesicular skin lesions Bacteriologic study of urethral and cervical smears and of the blood is usually diagnostic

15 *Chronic meningococcemia* (without meningitis) is characterized by arthralgias without inflammation, continued fever and by characteristic slightly tender, papulo-urticarial cutaneous lesions Several cases which I observed were confused with rheumatic fever because of the presence of arthralgias and a systolic murmur, and in one case a prolonged P-R interval (0 22 second) The meningococcus may be isolated from cutaneous lesions or from the blood stream but cultures should be observed for at least two weeks before they are discarded

16 *Undulant fever*, like the two preceding may be characterized by arthralgias and continued fever Positive blood culture or agglutination reaction and the history of contact with infected animals or the ingestion of unpasteurized milk or its products are diagnostic features

17 *Rat bite Fever (Haverhill Fever)* The rat-bite fever due to the Streptobacillus moniliformis is characterized by fever, polyarthritis and a morbilliform or petechial rash

(Haverhill fever) The diagnosis is made by culture of the causative organism from the blood stream

18 *Ileitis and ulcerative colitis* may simulate rheumatic fever since they are not infrequently characterized by arthralgias or arthritis fever and erythema nodosum while the diarrhea may be minimal and overlooked A careful history and sigmoidoscopic and roentgenologic examination of the intestinal tract disclose the true diagnosis

19 *Acute appendicitis* is occasionally diagnosed when abdominal symptoms are prominent in cases of rheumatic fever The difficulty of differentiation is avoided if a careful history and examination are undertaken

20 *Non rheumatic Forms of Cardiac Disease* The differential diagnosis is discussed in the chapters on valvular heart disease pericarditis and endocarditis

Among other conditions which occasionally simulate rheumatic fever are coccidioidomycosis and rarely actinomycosis [6]

PROGNOSIS OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

The prognosis of rheumatic fever will be considered under three headings (1) The acute attack of rheumatic fever (2) The probability and significance of recurrent rheumatic attacks and further cardiac damage (3) The course of chronic rheumatic heart disease

THE ACUTE ATTACK OF RHEUMATIC FEVER

Recovery [illegible] the rule in the first acute attack of rheumatic fever In a series of 20 000 reported cases Atwater[4] found a mortality of 1 7 per cent in the acute attack In the recent cooperative study there were [illegible] deaths among 500 children with acute rheumatic fever (1 2 per cent) [illegible] Death in acute rheumatic fever results from cardiac failure pericarditis pneumonia pulmonary embolization bacterial endocarditis and toxemia In more than 75 per cent of the cases active rheumatic disease is the basic cause of these fatal complications Hyperpyrexia has become a rare cause of death since the use of salicylates

Higher mortality rates occur in patients with *recurrent* acute attacks usually associated with carditis and cardiac failure than in those with their first attack The distinction between mortality in the initial acute attack and subsequent attacks [illegible] seen in the statistics of Hassler and Moller[44] Of 110 patients suffering their first attack of rheumatic disease is the basic cause of these fatal episode, whereas of the 35 in a recurrent acute attack 32 per cent died The latter group is small and the mortality rate unusually high but undoubtedly the seriousness of the disease and the fatality rate increase with new attacks

The *duration* of the initial or subsequent acute attacks is variable Mild cases may hardly reach the clinical horizon or may appear as a simple febrile respiratory infection with or without arthralgias disappearing in a week or two The more fully developed attack lasts three to twelve weeks This however merely represents the average period of obvious clinical manifestations A subclinical period of activity indicated by subfebrile temperature leukocytosis increased rate of sedimentation of red blood cells etc or recurrent exacerbations after brief quiescence may prolong the attack In a series of 54 cases studied by Bland[8] the average duration of active disease was eight months Persistent rheumatic activity or cardiac failure for longer than six months denotes a serious prognosis

Aside from those children who die in the acute attack an additional 10 to 20 per cent never really recover but are left with badly functioning hearts or run a subacute course with persistent rheumatic activity or frequent recurrences of activity at short intervals Such children remain invalids who spend the greater part of time in bed require repeated or constant hospitalization and die within two to six years usually before reaching adult life

Finally about 80 per cent of patients with rheumatic fever reach adult life Many of these have experienced mild attacks or the attack of rheumatic fever is overlooked and surmised later when rheumatic cardiovalvular disease is accidentally discovered About 65 per cent of children who have had rheumatic fever not only attain adult life but can lead relatively normal lives [illegible] either because they have no apparent cardiac disease or because the cardiac lesions are well compensated The remaining 15 per cent who reach adult life have limited cardiac reserve or definite congestive heart failure and form the bulk of cardiac patients seen in clinics and hospitals The exaggerated pessimism of statistical data on the prognosis of adult rheumatic heart dis

ease is largely due to excessive weighting by these unfavorable cases

THE PROBABILITY AND SIGNIFICANCE OF RECURRENT RHEUMATIC FEVER AND CARDIAC DAMAGE

Following recovery from the acute attack, the prognosis is dependent on (a) the probability of recurrences of rheumatic fever and (b) the cardiac damage caused by the first or subsequent attacks Both of these are closely related to the age at which the initial attack occurs When the initial attack appears before the age of 10, a recurrence is to be anticipated in 75 to 90 per cent of cases [9, 120] Thereafter the probability and number of recurrences diminish [11] and they become infrequent after the age of 20

According to Cohn and Lingg [22] *and this* has also been my experience recurrence is the rule before puberty and becomes strikingly less frequent thereafter Wilson and Lubschez,[120] as well as Ehlertsen,[33] stressed not only the age of onset as a determinant of subsequent rheumatic recurrence but also the interval of freedom following an acute attack Thus in children below the age of 14 there was an incidence of about 40 per cent of recurrence within one year after an attack of rheumatic fever as contrasted with a risk of recurrence of 11 per cent following one year of freedom Practically one may assume that recurrence is improbable when the first attack occurs after the age of 20 or if five or more years have elapsed since the last attack and the patient is past the age of 16 However, under the stress of military training, crowding and constant reexposure to new recruits rheumatic recur*rence was not uncommon in young adults who* had long been free of rheumatic activity The incidence of rheumatic recurrences is being sharply reduced by the prophylactic use of sulfonamides or antibiotics and the vigorous treatment of streptococcus A infections in rheumatic children (p 856)

The incidence of significant *cardiac damage* in the initial attack of rheumatic fever varies between 30 per cent and 80 per cent of cases according to the age at the initial infection Cardiac involvement is most probable when the first rheumatic attack occurs between the ages of 5 and 10 The probability of cardiac involvement diminishes as the age of initial infection increases and becomes particularly infrequent when the first attack of rheumatic fever occurs in adult life [28, 60] This may be due to error in the diagnosis of rheumatic fever in the adult (p 843)

The occurrence of *subcutaneous nodules* has usually been associated with concomitant carditis and therefore with an ominous prognosis [15] but Bland and Jones[10] observed a 37 per cent mortality among rheumatic children with subcutaneous nodules followed for twenty years as compared with a 63 per cent mortality among those who had had pericarditis *Rheumatic pericarditis* is serious both because of relatively high acute mortality and the probability of permanent cardiac damage In 135 cases of acute rheumatic pericarditis studied by Massie and Levine [70] there was an acute mortality of 16 per cent in an average period of 5 weeks, a further mortality of 30 per cent among *82 of these patients who were* followed for a subsequent average period of 6 4 years On the encouraging side was the remarkable finding that 36 per cent of those followed had no clinical evidence of organic heart disease Thomas et al [109] reported no mortality in 8 cases of dry pericarditis and 50 per cent mortality in 30 cases of rheumatic pericarditis with effusion A more serious outlook is indicated by the observations of Ash [4] who found that 75 per cent of 553 children with rheumatic pericarditis were dead after a follow up period of 9 6 years Other evidences of *carditis,* such as cardiac enlargement and diastolic gallop rhythm, but especially congestive heart failure are also associated with a very high acute mortality, or with a high incidence of severe and permanent organic heart disease

Chorea in itself does not denote an unfavor*able prognosis with respect to* the probability of cardiac involvement However, other rheumatic manifestations eventually develop in the majority of cases of chorea and the incidence of cardiac disease is determined by these other rheumatic features *Jones and* Bland,[66] in an analysis of 482 cases of chorea observed an incidence of only 3 per cent of heart disease among 134 patients with chorea alone while among 184 patients with chorea and other evidences of rheumatic fever, heart disease was discovered in 80 per cent *In a* subsequent twenty year follow up *of* 1000 cases of rheumatic fever there was only a 1[illegible] per cent mortality in that period[10] *among* patients who had had chorea with or without cardiac involvement

Considering the entire course of the disease, it is probable that 65 to 75 per cent of children who suffer from rheumatic fever develop clinical heart disease with their first or subsequent attacks [illegible] [illegible] [10] If electrocardiographic changes or slight cardiac enlargement associated with systolic murmurs are accepted as evidence of organic heart disease then at least 90 per cent of patients with rheumatic fever may be considered as developing rheumatic heart disease [113] The stricter the criteria for the initial diagnosis of rheumatic rever, the higher is the incidence of subsequent fheumatic heart disease

Of 1000 children and adolescents hospitalized for rheumatic fever and followed by Bland and Jones [10] 653 had had signs of rheumatic heart disease on recovery from the initial illness but after 20 years the signs of heart disease had disappeared in 103 (16 per cent) On the other hand of the remaining 347 patients who recovered from their initial illness without detectable heart disease at the time, 154 or 44 per cent had acquired signs of valvular heart disease in the period of follow up

THE COURSE OF CHRONIC RHEUMATIC HEART DISEASE

The outlook for the child with rheumatic heart disease is now regarded as less unfavorable than formerly In a study of 717 cases of rheumatic fever and heart disease Wilson[114] noted that 18 per cent had died within an average period of eight years after the onset of rheumatic fever Stroud, Bromer and associates,[105] in a similar study of 458 rheumatic children, found that more than 20 per cent were dead within ten years after the initial rheumatic attack and another 20 per cent were totally disabled, in a more recent ten year study from the same institution the mortality rate had fallen to 15 per cent [106] Martin[46] studied some 1400 children with inactive rheumatic heart disease over a twenty year period About 30 per cent were dead at the end of that period, 10 per cent having died after two years and 26 per cent after twelve years In a twenty year follow up of 1000 children and adolescents who were hospitalized for rheumatic fever between 1921 and 1931 Bland and Jones[10] found that 202 (20 2 per cent) had died after the first ten years and a cumulative total of 301 had died after twenty years Rheumatic fever and congestive heart failure accounted for 80 per cent of the fatalities and bacterial endocarditis for an additional 10 per cent All these studies disclose that the great majority of fatalities occur below the age of 20 and that 70 per cent of children contracting acute rheumatic fever survive to an average age of 35 to 40

The chief danger lies in the probability of acute recurrences with a concomitant increase in cardiac damage Each new attack brings with it its percentage of acute mortality of cardiac failure or of progressive cardiac damage Thus the difficulty of prognosis in childhood lies not only in evaluating the effect of existing cardiac damage on life expectancy but in predicting what further injury will be wrought by subsequent attacks

If the child shows evidence of *right heart failure* the prognosis is very poor, it is doubtful whether he will survive puberty The existence of persistent *atrial fibrillation* also warrants a serious prognosis in that it denotes extensive myocardial damage Atrial fibrillation in rheumatic cardiac children occurs in fatal cases and is usually a late development However, this must be distinguished from the adult cases of rheumatic heart disease in which atrial fibrillation may persist for fifteen years or longer

Signs of *persistent active rheumatic disease* in a child with rheumatic heart disease always call for a guarded prognosis This applies particularly to the cases in which there is prolonged active carditis On the other hand if there is no cardiac failure if the cardiac rhythm is normal and if all signs of active disease subside the prognosis as to the organic cardiac lesion is temporarily improved Practically it may be considered that the early prognosis is greatly improved when puberty is passed when there are no longer signs of active rheumatic disease and when five years or more have elapsed since the preceding attack When this period is continued into maturity and the cardiac lesions remain well compensated the prognosis becomes increasingly favorable Conscientious uninterrupted use of antibiotics to prevent and eradicate streptococcus A infections may greatly and favorably change the outlook

If rheumatic patients dying in childhood or up to the age of 20 are segregated in statistical studies from those who survive the age of 20, the much more favorable outlook for duration

of life in the latter is no longer obscured by the unfavorable statistics in the former

The problem confronting the pediatrician or cardiologist who must give a prognosis regarding a *child* with rheumatic heart disease is quite different from that confronting the physician who attends an *adult* rheumatic cardiac patient For the latter has already overcome the serious dangers which are associated with recurrent attacks or persistent rheumatic activity of childhood, and which are the very elements that make prognosis unfavorable in earlier life The very fact that these adult individual have come to maturity despite recurrent rheumatic attacks indicates that the functional and anatomic damage in these individuals was least serious If they come to maturity with well compensated rheumatic heart disease the outlook is quite favorable for many years

Of about 800 children and adolescents who survived at least ten years after their initial attack of rheumatic fever, approximately 700 (87 5 per cent) were still alive after an additional ten years [10] Of 644 patients studied by de Graff and Lingg[27] 46 lived for more than 30 years and some more than 40 years Longevity was also noted by Wilson and Lubschez[100] during thirty years of observation of 1042 children with rheumatic fever In a study of autopsies from a city home for the aged I found the average age of death from rheumatic heart disease to be 65 years [27] This is not an average figure for longevity in rheumatic heart disease, but indicates the possible outlook for some patients In a more recent clinical pathological study of 253 autopsies in cases of rheumatic heart disease,[69] there were 50 (19%) between the ages of 40 and 81 (average, 57 3)

CAUSES OF DEATH IN RHEUMATIC HEART DISEASE

In children with rheumatic heart disease death in the great majority of cases is due to active rheumatic disease with resulting pancarditis heart failure pneumonitis pulmonary infarction and toxemia

Among adults congestive heart failure is the commonest cause of death Bacterial endocarditis embolization pulmonary infarction and bronchopneumonia and atherosclerotic coronary occlusion with myocardial infarction are among the other causes of death

Sudden death is much less common than in cases of atherosclerotic coronary disease or cardiovascular syphilis Its most frequent occurrence is in patients with aortic stenosis Its advent in aortic insufficiency has been exaggerated owing to inadequate segregation of cases due to syphilis

THE TREATMENT OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

THE ACUTE ATTACK OF RHEUMATIC FEVER

1 Bed Rest

Absolute confinement to bed is a vital element of the treatment of the active stage of the disease This includes pleasant surroundings and facilities for diversion if possible A choice must be made between hospitalization and home care of the child [14] The actual facilities at home, the availability of nursing care, the ability of the mother to administer medication and other measures if a nurse is not available, and general economic and social factors contribute to this decision [38] Removal from home and parental attention may present psychic trauma On the other hand home care when there are siblings who are well and active has its disadvantages There is considerable disagreement as to the proper duration of bed rest It may be accepted as a general principle that this period should be at least as long as there is rheumatic activity (For signs and tests of rheumatic activity see p 842 See also discussion of steroid hormone therapy p 852)

2 Diet and Regimen

The principle of the *diet* is to maintain nutrition When there is moderate or high fever the diet must be limited to fluids only and these must be rich in calories Vitamins and minerals may have to be supplied in concentrated form

Because of evidence that the serum vitamin A and carotene levels are reduced in rheumatic fever, the administration of vitamin *A* has been recommended[112] during the acute and subacute stages Similarly vitamin *C* supplements have been suggested as desirable[14] Since most of the patients are growing children an adequate protein intake is essential As with other febrile diseases fluids should be forced (at least 2500 to 3000 cc daily) *It is* especially important in rheumatic fever when there is a large fluid loss through excessive perspiration In the presence of congestive heart failure an extremely low *sodium* diet should be given (p 239)

Cathartics or enemata may be necessary while the patient is in bed. Mild cathartics such as aromatic extract of cascara or milk of magnesia are usually satisfactory.

3 Drug Therapy

Salicylates. Stricker,[104] who first recognized the therapeutic value of salicylates in rheumatic fever, considered them to be a specific cure for the disease. Although their specificity is no longer accepted, prolonged usage has established their antipyretic and analgesic effects, their striking relief of joint pain and swelling, and their beneficial influence on the general well being of the rheumatic patient. These rapid and impressive therapeutic effects of salicylates are so characteristic that they have been considered diagnostically important. However, a similar response may occur in other febrile states and occasionally such improvement is lacking in definite cases of rheumatic fever.

Since Pribram's[83] observations it has been taught that salicylates do not reduce the duration of the active disease. More recent studies have also indicated that the duration of rheumatic activity and the hospital stay of salicylate treated and untreated patients did not differ significantly.[74] On the other hand, Illingworth et al[51] gained the impression that in a group of patients with rheumatic fever treated with salicylates, fewer children developed additional rheumatic manifestations such as subcutaneous nodules, fewer suffered recurrences of arthritis, apical diastolic murmurs or evidence of persistent cardiac involvement than the children in a control group of cases of rheumatic fever not treated with salicylates. The question is far from settled because of the varied duration of individual cases and because the statistics available are not uniform in their criteria for subsidence of activity.

It has long been taught that salicylates do not prevent cardiac complications and that pericarditis, heart failure, pleuropulmonary symptoms and subcutaneous nodules have frequently developed in rheumatic children under full salicylate dosage.[illegible] On the other hand, Coburn[72] has claimed that intensive therapy sufficient to maintain a continuous salicylate plasma level of at least 35 mg per 100 cc, instituted early in the acute phase of rheumatic fever, not only rapidly suppressed the disease but also reduced the incidence of polycyclic recurrences and residual chronic activity and prevented cardiac residua. These claims have been supported by Peters and by others[59, 87] and disclaimed by still others who have used Coburn's therapeutic regime.[3, 115]

Some recent experimental observations suggested that the therapeutic effect of salicylates depends on their stimulation of the adrenal cortex,[47] but this has been refuted on the basis of other studies.[99, 6]

Indication for Salicylates in Rheumatic Fever. In view of the effectiveness and in my opinion the superiority of prednisone and other adrenocortical hormones, the role of salicylates in the therapy of rheumatic fever is now uncertain. McEwen[73] advocated the administration of salicylates in rheumatic fever without evidence of carditis, but this policy runs the risk of delay in the use of the hormones, of which the chief advantage may lie in their ability to prevent permanent cardiac damage when administered early. Salicylates may be of benefit in preventing the "rebound" phenomenon if administered when the dose of cortisone-like hormones is being finally reduced and for two or three weeks after the hormones are discontinued. Finally, there may prove to be some advantage in the simultaneous use of salicylates and cortisone-like drugs throughout the treatment of acute rheumatic fever.[40]

Administration and Dosage of Salicylates. *Acetylsalicylic acid* is given in a dosage of 0.06 gm (1 grain) per pound of body weight daily in divided doses up to a maximum of 10 gm daily. I often start by administering 0.65 gm (10 grains) every four hours throughout the 24 hour period and increase the dose or frequency until the desired effect is obtained. If toxic symptoms appear, the dose is reduced. The dose which is effective and non-toxic is continued until there are no signs of clinical activity, the blood count and sedimentation rate are normal and (if this determination is available) the C-reactive protein is no longer present. Thereafter salicylates are gradually reduced and discontinued.

Sodium salicylate may be administered in slightly higher dosage.

Sodium bicarbonate is administered with salicylates either as half the dose of sodium salicylate or in equal doses with acetylsalicylic acid. The alkali serves to diminish gastric irritation caused by the salicylates. According to Peters,[3] the toxic effects of very large oral doses of salicylates can be prevented by the simultaneous administration of

twice the dosage of sodium bicarbonate in solution In patients with rheumatic carditis and congestive heart failure the possible danger of administering significant quantities of sodium must be taken into account

The *toxic manifestations* of salicylates[39] include tinnitus, deafness vertigo headache, nausea and vomiting, and occasionally diarrhea Although there is some direct gastric irritation the toxic gastrointestinal symptoms are due to salicylate action on cerebral centers More serious evidences of salicylate intoxication are dermatoses, excessive vomiting Kussmaul respiration due to acidosis, tetany due to hyperventilation, delirium, mania, hallucinations, coma and death[93, 43] Hyperventilation appears to be due to increased sensitivity of the respiratory center to carbon dioxide and hydrogen ion produced by salicylates[1] This results usually in *respiratory alkalosis*[108] *But respiratory acidosis* may develop when respiration is inadequate[105]

Severe dyspnea from excessive doses of salicylates has been attributed either to fixed acid acidosis or medullary respiratory stimulation[49]

Hypoprothrombinemia may occur temporarily after a few days of intensive salicylate therapy[81] but with possible rare exception, it is insufficient to produce hemorrhagic phenomena

Corticotropin (ACTH) and Adrenal Cortical Hormones *Effect in Rheumatic Fever* The early dramatic report of Hench et al[46] on the beneficial effects of cortisone in acute rheumatic fever has been confirmed by numerous observers[63, 73] similar results have been observed with corticotropin, hydrocortisone and prednisone (Meticorten)[82] Within 12 to 48 hours following adequate doses of these hormones the fever subsides, joint pains and swellings diminish markedly or are completely alleviated and general toxicity abates Favorable but inconstant influence of these steroids has been noted with respect to the clinical evolution and subsidence of erythema marginatum[65, 73] and rheumatic subcutaneous nodules[17, 11, 119, 91]

There is a general impression that subcutaneous nodules resolve more rapidly on cortisone therapy than they would otherwise Histologic studies of nodules studied before and after the administration of such hormone therapy have indicated a striking diminution in inflammatory cellular elements following the hormone,[81, 77] although there are similar discordant studies by others[15, 8] Considerable interest is attached to the effect of these hormones on the subcutaneous nodules because of the similarity of the proliferative as well as exudative inflammatory lesions in the nodules to the more important lesions in the heart

Relative Effectiveness of ACTH Cortisone and Salicylates Six centers in the United Kingdom, five in the United States and one in Canada collaborated in a well controlled trial of the relative merits of ACTH cortisone and aspirin in the treatment of 497 patients with acute rheumatic fever and in the prevention of rheumatic heart disease in children under the age of 16 One year after the completion of treatment they reported that with minor differences there was no essential superiority of *any one of these agents over the others* None of the three agents resulted in uniform termination of the disease and, with all three agents, some patients developed fresh manifestations during treatment Treatment with the hormones resulted in more prompt control of certain acute manifestations, such as subcutaneous nodules, but this was balanced by a greater tendency for acute manifestations to reappear for a limited period when the six weeks course of treatment was discontinued At the end of one year there was no significant difference in the three treatment groups with respect to the cardiac status

Despite these findings ACTH cortisone and related hormones appear to be definitely superior to salicylates in the treatment of rheumatic fever None of the agents was found superior to the others in the restricted dosage employed in the cooperative study, in the control of the acute manifestations of the *average case* of rheumatic fever The superiority of the hormones becomes readily apparent only in the severely ill patient with rheumatic pericarditis high fever and frequent concomitant carditis and heart failure *provided adequate doses are employed* Pericarditis was present in 10 per cent of the cases in the United States 5 per cent of those in the United Kingdom The dosage of hormones in the United States cases was distinctly below optimal for pericarditis and even lower in the United Kingdom where more of the cases of pericarditis were treated

Similarly, heart failure occurred in about 10 per cent of the cases presumably essentially the same as with pericarditis Furthermore by chance there were about half as many cases with heart failure and pericarditis treated by aspirin as by ACTH and cortisone These data are mentioned to indicate that there were relatively few very severe cases which would test the advantage of hormones over salicylates and the minority of these were subjected to salicylate therapy In summary the comparative study could not demonstrate superiority of the hormones over salicylates because (1) suboptimal doses of the hormones were used especially for severe cases (2) therapy was discontinued too soon, (3) too few very severe cases of pericarditis and heart failure were treated

Effect of ACTH and Cortisone in Preventing Cardiac Damage Whereas the therapeutic efficacy of cortisone and corticotropin with respect to the acute inflammatory manifestations of rheumatic fever appears established, there is still uncertainty as to their possible benefit in preventing permanent cardiac damage as denoted by chronic valvular disease and cardiac enlargement Obviously patients suffering from their first attack of rheumatic fever, i e without previous cardiac disease are most suitable for evaluating such possible benefit of cortisone and corticotropin In the series of cases of Roy et al only 2 (6 5 per cent) of 31 patients treated within 7 days of their initial attack of rheumatic fever were left with significant murmurs whereas there were persistent murmurs in 17 (49 per cent) of 35 patients first treated between the eighth and fourteenth days in 22 (66 per cent) of 33 patients first treated between 2 and 4 weeks after onset in 15 (75 per cent) of 20 patients first treated between the fourth and sixth week, and in 36 (90 per cent) of 40 patients first treated after the sixth week In the same review of reported cases there is evidence that a reduction or disappearance of cardiac enlargement is most apt to occur the earlier hormone treatment is begun Other studies suggest that permanent myocardial damage is most likely to be prevented with *very high dosage* as well as *early administration* of these hormones [73, 45, 31, 40, 65, 78] Most studies thus far reported do not concern large enough groups of cases in which these treatment criteria are satisfied but the results are promising in regard to the possibility of avoiding chronic cardiac disease On the other hand, Harris et al [4] in a controlled study of 100 cases of rheumatic fever found no evidence that ACTH or cortisone favorably influenced cardiac manifestations regardless of the dosage or time of beginning treatment To counter this is the report of Wilson and Lim[1] showing a remarkable reduction in residual cardiac damage and an abbreviation in the duration of active carditis in patients treated with adrenocortical hormones for only seven days

Treatment Schedule Prompt hormone treatment is essential Prednisone (Meticorten) or prednisolone is administered in a minimal daily dose of 60 mg (20 mg or four tablets every eight hours) orally If necessary this dose is increased until a satisfactory response is attained Occasionally in very ill patients 100 mg of corticotropin is administered daily in a slow intravenous drip of 5 per cent glucose in distilled water for several days if necessary to obtain the desired clinical response If oral medication cannot be taken and intravenous corticotropin is not essential hydrocortisone can be given intravenously or intramuscularly in daily doses of 300 mg Oral medication is begun as soon as it is tolerated The daily dose of prednisone (60 mg in divided doses) is continued for four weeks provided the clinical course is satisfactory with respect to fever arthritis and laboratory findings Thereafter the dose may be diminished by 2 5 mg or one half tablet daily, but the previous effective dosage is resumed if symptoms and signs recur I prefer a schedule in which the dosage is reduced by 15 mg or three tablets daily at five-day intervals because the effect of a diminished dosage is often apparent only after this period

Clinical progress and activity of the disease are measured by the control of clinical features and determination of the erythrocyte sedimentation time and if available by the C reactive protein These laboratory tests usually do not return to normal for two to four weeks It is uncertain whether their return to normal is due entirely to suppression of rheumatic inflammation or to the effect of the hormones on the plasma proteins which influence these laboratory tests However, neither subsidence of clinical manifestations nor the disappearance of leukocytosis and C reactive protein and return to normal sedi

mentation rate denote that the basic rheumatic disease is inactive so long as the hormones are being administered

As a rule, the hormones are discontinued after eight to twelve weeks of treatment provided there are no clinical or laboratory signs of activity If the drugs are omitted too soon, e g , after only a week or two following suppression of the clinical picture and laboratory signs there is usually a reappearance of the florid manifestations of active rheumatic fever until treatment is resumed This represents a relapse or recrudescence of rheumatic fever On the other hand if treatment is discontinued after six to eight weeks or more of suppression of the disease mild fever, increased sedimentation rate and a positive test for C-reactive protein may reappear, persist only two or three days and disappear spontaneously. The latter occurrence has been termed a "rebound" phenomenon and has been interpreted as the response to mild residual rheumatic activity which becomes apparent when exogenous hormone has been discontinued and the patient's own inhibited adrenal cortex has not yet resumed its normal activity A similar rebound has been reported after discontinuation of salicylate treatment of rheumatic fever[35] In practice, the reappearance of rheumatic phenomena after at least six weeks of suppression by adequate dosage of the hormone should be regarded as a "rebound" and hormone should be withheld for at least five days unless the clinical features are severe Increasing severity and persistence of manifestations beyond that interval would denote an actual relapse and the need for resuming hormone therapy The administration of salicylates together with the hormones when the dosage of the latter is being diminished and continued salicylate therapy for two or three weeks after discontinuation of cortisone or related drugs may avert the rebound phenomenon Any frank relapse following suppressive therapy with salicylates or steroid hormones usually occurs within a week or two and virtually always within two months after discontinuing therapy[10] Thereafter the reappearance of rheumatic fever is associated with immunologic evidence of a new streptococcal infection[102] and therefore indicates a recurrent attack of rheumatic fever rather than a relapse

When ACTH, cortisone or hydrocortisone is administered in high dosage, sodium intake should be restricted to 50 to 200 mg daily A more liberal sodium allowance or no sodium restriction may be permissible when prednisone (Meticorten) is employed, provided there is no evidence of heart failure Evidence of sodium water retention or congestive heart failure should be combated by digitalization a low sodium intake and injections of mercurial diuretics To counteract possible potassium depletion due to the hormone especially when the latter is given in combination with mercurial diuretic therapy, enteric coated tablets of potassium chloride 1 gm two or three times daily, or 1 teaspoonful of potassium triplex (Lilly) may be given three times daily In addition antibiotic therapy should be administered at the onset for ten days to eradicate any living group A streptococci in the upper respiratory tract and thereafter continuous administration of prophylactic doses of sulfadiazine or penicillin should be undertaken (p 857), at the same time that hormone treatment is administered

Toxic or side effects of cortisone and related hormones include moon face weight gain with abnormally located fat deposits acneiform eruption hirsutism, and, with some of the hormones sodium water retention Less common effects include glycosuria, pigmentation striae, enlargement of the liver (fatty liver) peptic ulcer, and psychiatric complications As a rule all these manifestations except occasionally the psychiatric disappear when the hormone is discontinued However, Smith and Good[93] reported an alarmingly high incidence of important side actions in 11 children with rheumatic fever treated for a long time with high doses of prednisone (up to 100 mg per square meter body surface area per day for 40 to 171 days) Osteoporosis and compression fractures occurred in 3 In 9 patients there were marked and prolonged 'rebound phenomena ' In 5 of these there occurred a peculiar syndrome lasting 4 to 14 days characterized by intense pruritus and painful cutaneous lesions like erythema nodosum Two children developed panniculitis Two developed congestive heart failure without other clinical evidence of rheumatic fever, 9 to 60 days after cessation of prednisone therapy In one fatal case perivascular inflammation fibrinoid occlusion of multiple venules and subcutaneous fat necrosis, but no evidence

of active rheumatic carditis was found at autopsy

Aminopyrine Aminopyrine is quite effective in rapidly reducing fever and relieving the joint symptoms of rheumatic fever It possesses the advantages of producing neither the local gastric irritation nor the toxic effects of salicylates and does not require the simultaneous administration of sodium bicarbonate but there is danger of agranulocytosis in sensitive persons

The dose of aminopyrine is about one third that of the salicylates In *adults* 2 to 3 gm daily may be given in divided doses at four hour intervals in children 1 5 to 2 gm daily [96]

Digitalis is indicated and effective in the treatment of acute rheumatic fever when there is associated heart failure with or without atrial fibrillation Its administration in children is discussed on page 261 Sutton and Wyckoff[107] have reported beneficial effects in children with right sided congestive heart failure active rheumatic infection and normal sinus rhythm similar favorable results with digitalis were obtained by Walsh and Sprague[111] and Nadas and associates [80] Often the therapeutic effects are not striking or are absent and the rapid heart rate is unmodified because of the activity of a severe rheumatic disease Furthermore for the same reason there is a tendency to increase the dose of digitalis to dangerous levels, there are frequent instances of digitalis toxicity including the production of premature beats heart block atrial fibrillation ventricular tachycardia or even fibrillation

Mercurial diuretics should be administered when heart failure is present as discussed in Chapter 11 The usual dose in children is 0 5 to 1 cc

Oxygen therapy is indicated in the presence of severe respiratory distress or cyanosis due to pulmonary infarction or pneumonitis or to heart failure with pulmonary congestion or pulmonary edema

Morphine is rarely indicated and should be administered with caution It is occasionally desirable for the intense dyspnea of acute pulmonary edema or for very severe pain at the onset of rheumatic fever before salicylates or hormones become effective Codeine may be needed to control precordial pain or cough Sedatives or soporifics are frequently beneficial during the most acute phases of the disease

Antibiotics Sulfonamides and Penicillin (see Prophylaxis p 856)

CONVALESCENCE AND REHABILITATION

Convalescent Homes and Sanatoria

Convalescence does not properly begin until all signs of rheumatic activity have disappeared Discharge from a hospital ward to make room for more acutely ill patients does not necessarily denote that the rheumatic patient is ready for convalescence Neither does removal to a convalescent home label the patient as convalescent if he still shows active rheumatic disease So long as there is activity the patient is properly a bed patient

In cognizance of the problems of the rheumatic child organizations in this country and in England have undertaken to care for convalescent cardiacs in special convalescent homes or hospitals In such institutions there are not only the advantages of continued and prolonged medical and nursing care for the patient but also opportunities for controlled study of the disease for research for prophylactic treatment and for the early discovery and treatment of rheumatic reactivations In addition the patient receives instruction in the rules of hygiene the psychologic advantages of group play and exercise schooling and occupational therapy during the intermediate period between active illness and the resumption of a relatively normal life

Resumption of Physical Activity

Physical activity may be resumed during convalescence but it should be increased more gradually than after other febrile diseases As a rule physical activity is not undertaken until there has been a two week period during which in the absence of suppressive drugs *there is no fever carditis arthritis or other* clinical or laboratory evidence of rheumatic activity On the other hand these strict criteria may necessitate such prolonged bed rest that cardiac anxiety neuroses are induced

Ordinarily the rate of progress of physical activity is determined in part by the presence and extent of cardiac damage and especially by the clinical response of the patient to increasing activity Various exercise tests have been employed to gauge progress and as a guide to the degree of activity permissible With the aid of a step-test Karpovich and associates[55] devised a program of physical reconditioning for soldiers convalescing from rheumatic fever Graded exercises were given

according to the response to the exercise test. They were able to begin these exercises safely within two weeks after clinical cessation of rheumatic activity and to reduce the conventional delay in beginning reconditioning from an average of 77 to an average of 16 days without any increase in cardiac damage.

TREATMENT OF THE CHRONIC INACTIVE STAGE OF RHEUMATIC HEART DISEASE

Essentially this involves the management of patients with rheumatic valvular heart disease (Chapters 26 to 29). When atrial fibrillation, heart failure or bacterial endocarditis develops, treatment follows the principles set down elsewhere under those headings. Aside from these and other complications the *patient with inactive rheumatic cardiovalvular* disease may rarely seek medical attention, and then only for some unrelated condition. Treatment during this period consists of instruction in hygienic living, avoidance of streptococcal and other infections, advice as to sociologic and economic problems, and, not the least, optimistic encouragement.

Exercise

When the stage of convalescence is passed and circulatory compensation is attained, the problem of exercise is not formidable. Restriction of physical exertion, formerly stressed as a vital point in the treatment of inactive heart disease, does not appear warranted when there is satisfactory compensation. For some time after an acute attack, a moderate degree of dyspnea, tachycardia and palpitation may result purely from prolonged bed rest and lack of physical training, independent of cardiac disease. Prolonged overprotection from physical exercise, even after rheumatic activity has ceased, serves only to protract the abnormal symptoms produced by even slight exertion. Except for the most rigorous sports involving unusual speed and endurance, such as rowing, long distance running, tennis, I do not believe it important or wise to restrict the well compensated inactive rheumatic cardiac patient. A moderate degree of consistent physical activity is of advantage in bringing about the efficiency of circulatory, respiratory and metabolic economies which result from training and which would appear to be of special value to the cardiac patient. So long as there are no evidences of circulatory failure, moderate exercise is of as much value to the rheumatic cardiac as to the normal person. The degree and amount of exercise permitted depends on the individual's symptomatic response, undue fatigue and dyspnea being the stop signals.

Prophylaxis

Antibiotic Treatment of Group A Streptococcus Pharyngitis.[84,85,51,21,13] Active antibiotic treatment of Group A streptococcus infections and prevention of such streptococcal infections with the aid of antibacterial agents have recently become the most aggressively employed measures in the prophylaxis of rheumatic fever. Such treatment is based on the current widespread belief that the Group A streptococcus is the inciting agent in the initial attack of rheumatic fever and its recurrent activations.

It is strongly urged that all attacks of Group A streptococcal infection of the upper respiratory tract in children be vigorously treated with antibiotics which are capable of completely eradicating the streptococci. Routine throat cultures are impracticable but the diagnosis can often be made on such clinical criteria as sudden onset of fever, soreness of throat, especially on swallowing, intense redness of the pharyngeal mucosa and pharyngeal exudate, and cervical lymphadenitis. In one series, an accurate diagnosis of streptococcal sore throat was attained in 70 per cent by clinical criteria alone.[1] Antibiotic therapy for streptococcal sore throat should be given at least to all children between the ages of 4 and 14, and up to the age of 21 in those who have had a previous attack of rheumatic fever.

Treatment should begin as early as possible, preferably within 48 hours, and continued for ten days; however, there is evidence that rheumatic fever may be prevented by such treatment even when administered as late as the ninth day after the onset of the streptococcal infection.[20]

Penicillin, chlortetracycline (Aureomycin), oxytetracycline (Terramycin), tetracycline (Achromycin) and erythromycin are equally beneficial in their clinical effect on acute streptococcal sore throat. But for the prevention of rheumatic fever the streptococci must be actually eliminated. This is accomplished by penicillin and probably by erythromycin, but less certainly or consistently by the other antibiotics. Studies of the efficacy of various antibiotics in the actual prevention of rheumatic fever showed that penicillin reduced

attacks of rheumatic fever by 91 per cent[114] chlortetracycline by 74 per cent[82] and oxytetracycline by 66 per cent[11] but the differences may be due in part to differences in relative dosage and duration of drug administration Other studies have shown that adequate penicillin treatment of hemolytic streptococcal sore throat has reduced the incidence of clinically overt rheumatic fever by 95 per cent or more[29 31]

Penicillin may be administered as a single intramuscular injection of *600 000 units of benzathine penicillin (Bicillin)* in children or 900 000 in young adults Adequate penicillin levels are maintained for the desired period[114 11 31] Or *300 000 units of aqueous procaine penicillin* may be given daily intramuscularly for ten days or procaine penicillin with aluminum monostearate in oil 300 000 every third day for 3 doses in children, or 600 000 every third day for 3 doses in young adults Or *400 000 units of buffered penicillin* may be given orally twice daily for ten days Oral doses of 500 000 to 1 million units of penicillin daily have been found effective in the care of streptococcal pharyngitis and in eradicating the carrier state by several groups of investigators[82 113] Chlortetracycline oxytetracycline tetracycline or erythromycin[4] 2 gm daily in divided dosage should be reserved only for those who are hypersensitive to penicillin until its consistent bactericidal effectiveness is established Sulfonamides are unsatisfactory since they are bacteriostatic and they do not completely eradicate the hemolytic streptococci

Antibacterial Prophylaxis against Group A Streptococcal Sore Throat[84 88 100] Continuous maintenance of antistreptococcal prophylaxis has been effected by the use of the sulfonamides oral penicillin or long acting penicillin (benzathine penicillin) in patients known to have rheumatic fever Prophylactic antibacterial therapy should be maintained for a period of five years after the last attack of rheumatic fever or preferably prophylaxis should be maintained to the age of 25 Studies of bacterial throat flora during chemoprophylaxis of rheumatic fever have thus far shown no evidence of danger of secondary bacterial or fungal complications[75]

Sulfonamide Prophylaxis Sulfonamides have been found to diminish sharply the occurrence of streptococcal infections including scarlet fever[116] and to reduce the incidence of rheumatic fever recurrence by 80 to 90 per cent[89] The sulfonamides possess the advantage of easy administration good absorption and inexpensiveness Toxicity including fever nausea vomiting dermatoses and leukopenia (rarely agranulocytosis) occurred relatively frequently after sulfanilamide but much less commonly since the use of sulfadiazine or Gantrisin[16 89] Sulfonamide resistant strains have developed and caused outbreaks of pharyngitis as a result of mass prophylaxis in military establishments but this is rare and may be controlled by shifting to other antibiotics Finally the sulfonamides are bacteriostatic and merely suppress hemolytic streptococcal infections Unless sulfonamide prophylaxis is continuous throughout the year, there is a rapid reappearance of hemolytic streptococci in the pharynx or nasopharynx when sulfonamides are discontinued If a hemolytic streptococcal infection has occurred the streptococci should first be eradicated with penicillin before sulfonamide prophylaxis is initiated

Sulfadiazine or Gantrisin is administered orally in a daily dose of 0 5 gm for those below 60 lbs and 1 gm daily for those above that weight[16] It is given throughout the year Continuous therapy is more likely to be carried out conscientiously if the daily dose is given as a single dose each morning

Penicillin Prophylaxis *Oral Penicillin* Oral buffered penicillin, 200 000 to 250 000 units is given once daily preferably before breakfast It has been shown that once hemolytic streptococci have been eliminated from the throat by larger doses of penicillin prophylaxis against streptococcal infection and consequent rheumatic recurrences can be effectively carried out by small continuous doses of oral penicillin[48 47 122 7]

Toxic reactions are very uncommon (0 5 to 2 per cent[7 113]) and usually mild There may be urticaria angioneurotic edema and rarely a reaction similar to serum sickness The disadvantages of oral penicillin prophylaxis include uncertain absorption of the penicillin its costliness and the difficulty of maintaining uninterrupted prophylaxis[100]

Repository Penicillin A single intramuscular injection of 1 200 000 units of benzathine penicillin (N N -dibenzylethylenediamine dipenicillin G) is capable of eradicating hemolytic streptococci from carriers and when repeated once every four weeks prevents

recurrences of Group A streptococcal pharyngitis and of rheumatic fever [30, 103, 72, 77] The choice between oral penicillin and benzathine penicillin intramuscularly will depend on personal preference as between daily continuous oral medication and monthly injections their relative costs and especially on the routine which is most likely to be followed conscientiously

In summary any attack of Group A streptococcal pharyngitis in rheumatic individuals should be treated with 400,000 units of oral penicillin two times daily for 10 days or with one intramuscular injection of 600 000 to 1 200,000 units of benzathine penicillin (Bicillin) Prevention of further streptococcal infections in the individual with previous rheumatic fever or rheumatic heart disease should be undertaken by administering 0 5 to 1 gm of sulfadiazine or Gantrisin daily, 250 000 units of oral penicillin or oral benzathine penicillin daily or 1 200,000 units of benzathine intramuscularly once a month until the age of 25, or for at least five years after the last attack of rheumatic fever

Psychotherapy

Few things are more terrifying than the sense of impending doom which comes to an individual when he learns that he is suffering from heart disease But experience with other chronic illnesses beginning in youth, such as diabetes and tuberculosis has demonstrated the advantages of teaching patients to understand their illness and of enlisting their valuable cooperation Cooperation of the parents, physician psychiatrist and social worker is often necessary to aid the child in adjusting to his physical incapacity during his illness, to the frequent need to be in a hospital away from home, to the prolonged limitation of activity during convalescence and possible restrictions thereafter, and to the threat of a permanent handicap and a shortened life [57, 8]

Whenever the patient appears either for follow-up examination or for incidental extracardiac complaints so long as the heart is functioning satisfactorily, the physician should not overlook these opportunities for commenting on how well the heart is behaving Such encouragement is of prodigious value to the patient s mental outlook, while failure to comment may leave him with a sense of prolonged depression and with neurotic symptoms Only occasionally one encounters a patient who is in no danger of a neurosis but who must be struck with the fear of imminent death in order to obtain the mildest degree of cooperation

The well compensated rheumatic cardiac may suffer from a variety of symptoms particularly aches and pains and abdominal distress which are really of a functional nature but which he fears may be related to his cardiac disease Reassurance as to his cardiac status and discovery of the basis of the symptoms generally lead to their control

Advice on Occupation, Marriage Pregnancy and Childbirth

The rheumatic cardiac usually reaches the chronic inactive stage of his disease at an early age Thus he often expects from his physician advice as to the choice of a suitable occupation and as to marriage Married women patients want to know the dangers of pregnancy and childbirth Unfortunately the choice of an occupation is not a free one but is conditioned by social and economic factors, and by chance as well as by ability and opportunity for training To the extent that choice is possible the occupation chosen should permit control of hours of work and working conditions This usually means self employment either as a business proprietor or in some profession When employed by others the work should not entail long or irregular hours severe physical or mental stress, or exposure to dampness drafts extremes or sudden changes of temperature or undue crowding The education and cooperation of employers in the most efficient use of rheumatic cardiacs should be helpful The establishment of work classification units has been of great value in rehabilitating the rheumatic as well as other cardiac patients with respect to restoring them to the most suitable gainful employment [21a, 8a]

The patient s question as to the advisability of marriage is usually a rhetorical one Generally the patient comes for advice when marriage is already pending and then he comes only for acquiescence in his decision The physician s task can only be to evaluate the patient's cardiovascular status and to inform him as to the probable outlook in terms of that status and available limited knowledge of prognosis

Pregnancy and *childbirth* are discussed in Chapter 47

THE TREATMENT OF CHOREA

This is essentially a problem in *nursing care*. It is important to maintain nutrition, avoid overstrain and injury, assure cleanliness of the mouth and skin and obtain as much mental and physical comfort as possible. Rest in a bed with sideboards is obligatory if there is marked loss of motor control. The sideboards as well as the head and foot supports should be well padded. Special attention to the patient's needs for defecation or urination is necessary, especially if the child cannot make his desires known because of speech disturbance. The nurse will look for sores, injuries, toothache, etc., which the patient cannot reveal by speech and which may serve to exaggerate his mental and emotional irritability. Patience and encouraging assistance are invaluable in feeding the child if the all important nutrition is to be maintained. When this is too difficult or too trying for the patient, it is wise to resort to nasal feeding.

Sedatives are useful to reduce exaggerated activity in the daytime and to obtain sleep at night.

Salicylates are often employed but are not indicated unless there is fever or arthritis. The effect of adrenal cortical hormones is not yet established but they have appeared to be beneficial in a number of cases and are worthy of trial. After many years of use of Nirvanol and/or artificial pyrexia the value of these therapeutic agents remains unproven.

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Chapter 34

BACTERIAL ENDOCARDITIS

Bacterial endocarditis is a disease due to bacterial infection of the valvular and mural endocardium The causative organisms can usually be demonstrated during life by blood cultures, and post mortem by spreads of the endocardial vegetations The clinical picture is that of a general infection (septicemia) with endocardial embolic and local vascular symptoms of variable prominence Detailed descriptions may be found in the publications of Osler [145] Schottmuller [173] Libman [118] Blumer [11] Thayer [184] Perry [150] Libman and Friedberg [122] and Kerr[109]

Bacterial endocarditis is a frequent and important cardiac ailment ranking in incidence next to coronary hypertensive and rheumatic heart disease In many localities it is encountered much more frequently than cardiovascular syphilis Its frequency in various localities depends on the frequency of rheumatic heart disease of which it is usually a complication Bacterial endocarditis was reported to develop in about 10 to 25 per cent of the cases of rheumatic heart disease [22] [89] In the series of 1000 patients with rheumatic heart disease followed by Bland and Jones,[10] 10 per cent of 202 fatalities were due to bacterial endocarditis

Bacterial endocarditis was formerly subdivided into acute and subacute bacterial endocarditis of which the latter was much more common In general the cases were considered to be acute if their duration was less than six weeks and subacute if longer than that period This division is not a sharp one because the time of onset is usually difficult to establish and because there is considerable overlapping in the clinical bacteriologic and pathologic features of the two forms On the other hand this classification was not entirely arbitrary because the acute and subacute cases are generally due to distinctly different organisms Occasionally organisms usually associated with the acute disease produce a subacute bacterial endocarditis and those generally associated with the latter may produce an acute bacterial endocarditis The acute and subacute forms usually present distinct pathologic and clinical differences which justify their separation In general in subacute bacterial endocarditis the original focus is uncertain or practically asymptomatic and the clinical picture is due essentially to the endocardial lesions and their complications In acute bacterial endocarditis the endocardial infection is often secondary to a gross apparent focus (often of a surgical nature) or to some other primary disease with bacteremia, and the clinical picture of the endocarditis is dominated and obscured by the initial focus and the bacteremia As early diagnosis and effective treatment have become more widespread the distinction between acute and subacute bacterial endocarditis is becoming academic Nomenclature should be based on the etiologic agent e g Streptococcus viridans endocarditis gonococcal endocarditis, and so on

ETIOLOGY

CAUSATIVE ORGANISMS

Bacterial endocarditis is due, in about 95 per cent of cases, to (1) the Streptococcus viridans (salivarius mitis), (2) the Streptococcus fecalis (enterococcus) or (3) the Micrococcus (Staphylococcus aureus or albus)

Non Hemolytic Streptococci Streptococcus Viridans

Streptococci are classified according to their effects on blood agar plates [176] The streptococci producing colonies surrounded by a clear zone of hemolysis are termed hemolytic or beta streptococci They are virtually identical with Group A or D streptococci according to the classification of Lancefield [114] They correspond to the long-chained Streptococcus pyogenes of former terminologies, which may

cause an acute bacterial endocarditis but very rarely the subacute form Streptococci forming colonies without a sharp clear zone of hemolysis are termed non hemolytic streptococci and subdivided into *Streptococcus viridans or alpha* if the colony is surrounded by a zone of greenish discoloration with or without partial hemolysis, and *Streptococcus anhemolyticus or gamma* if there is neither greenish discoloration nor hemolysis around the colonies on blood agar plates

Varieties of Non hemolytic Streptococci Of the non hemolytic streptococci responsible for subacute bacterial endocarditis, the Streptococcus viridans causes most cases but gamma streptococci (sometimes called indifferent streptococci) may also cause the disease The Streptococcus viridans (alpha) is the organism frequently found in the oral cavity and was therefore formerly termed the Streptococcus salivarius Another organism of the oral cavity termed Streptococcus mitis is also a Streptococcus viridans Loewe Plummer and associates[128] segregated a special non hemolytic streptococcus which they termed Streptococcus s b e and which was responsible for 40 out of 115 consecutive case of subacute bacterial endocarditis This organism produced greening on blood agar in 24 hours hydrolyzed arginine in 48 hours, fermented inulin in a week and did not produce large mucoid colonies on sucrose agar

The non hemolytic streptococci are characterized by a low degree of virulence in contrast with the microorganisms usually responsible for acute bacterial endocarditis The former are generally common saprophytic inhabitants of the mouth, upper respiratory and gastro intestinal tract and possess a low pathogenicity for laboratory animals The usual habitat of the Streptococcus viridans in the naso pharynx and oropharynx, and often in infected tonsils and apices of infected teeth, suggests that most of the cases of subacute bacterial endocarditis result following accidental passage of this organism from the oral or pharyngeal cavity into the blood stream

Streptococcus Fecalis (Enterococcus) (p 875)

A special group of non hemolytic streptococci which are responsible for bacterial endocarditis with increasing frequency are the enterococci These are usually of the gamma type of streptococcus, and because they are commonly found in the intestinal tract are often called Streptococcus fecalis Streptococcus liquefaciens, Streptococcus durans and Streptococcus zymogenes are other species of enterococci The enterococci have been characterized by their heat resistance (60° for thirty minutes), by their fermentation of esculin which is turned black, and by their growth in the presence of 6 5 per cent sodium chloride They usually appear in pairs of ovoid cocci, or occasionally in short chains Unlike the Streptococcus viridans, the enterococcus ferments mannitol The enterococcus is of special interest because it is often much more resistant to penicillin than the Streptococcus viridans When classified serologically according to typo-specific carbohydrate antigenic substance the enterococci are found to fall in the Group D streptococci of Lancefield[1?] *On the other hand, the alpha streptococci* (viridans) fall into a number of species of types, some of which belong to Group D

Staphylococci (Micrococci)

Concomitant with the increase in resistant strains of staphylococci (micrococci)[178] more and more cases of staphylococcus endocarditis are being encountered Staphylococci have been reported as the cause of bacterial endocarditis in 2 to 28 per cent of reported series of cases (p 875) In my experience they account now for at least 10 per cent of cases, but the actual incidence may be less because a disproportionate number of patients with endocarditis due to staphylococci are apt to be seen by a consultant or in a teaching hospital

Other Causative Organisms

About 5 per cent of the clinical cases of bacterial endocarditis are due to a great variety of microorganisms other than the Streptococcus viridans, Streptococcus fecalis or micrococci[181]

One group is composed of the *virulent, so-called pyogenic organisms* which tend to cause distinctive lesions and either an acute or subacute clinical course These organisms include the hemolytic streptococci (Lancefield's group A) pneumococci, Neisseria gonorrhoeae,[134] N meningitidis,[51] E coli[56] Aerobacter aerogenes, [183] B proteus Salmonella organisms[193, 181] the *paracolon bacillus*[?] Gaffkya tetragena[13] *Pseu*domonas aeruginosa (B pyocyaneus)[137] *Kleb*siella pneumoniae (Friedlander's bacillus), pi rilla and B anthracis The causative staph ylococci streptococci A or pneumococci are usually aerobic but may be anaerobic[1?] The several varieties of organisms responsible for brucellosis (undulant fever), i e, Brucella

abortus melitensis and suis may also cause subacute or occasionally acute bacterial endocarditis [60] [illegible]

Another group of causative organisms are common *saprophytic inhabitants* of the human body but which by chance invade the blood stream and may produce bacterial endocarditis if they find conditions favorable for localization and growth on the cardiac valves These organisms include the *Hemophilus influenzae*[163] and parainfluenzae[31] the gram negative *Neisseria pharyngis group*[97] (N pharyngis sicca N catarrhalis and N flava) and the *Corynebacteria* (diphtheroids) Like the nonhemolytic streptococci most of these are common saprophytes of the upper respiratory tract and oral cavity Diphtheroids must be distinguished from a diphtheroid phase of a nonhemolytic streptococcus

Joachim and Polayes[97] observed the development of subacute bacterial endocarditis due to a yeast (*Candida or Monilia parakrusei*) in a morphine addict who had injected intravenously a contaminated solution of morphine Similar cases of mycotic endocarditis were documented by others[209, 113, 200] There are other reports of subacute bacterial endocarditis due to higher bacteria yeasts or fungi,[8] including cases due to Actinomyces bovis[201] and Histoplasma capsulatum[75] A variety of special media and techniques may be necessary to isolate the causative organisms in these cases The Erysipelothrix rhusiopathiae of swine erysipelas may cause erysipeloid and a complicating subacute bacterial endocarditis in humans who handle infected fish or who make buttons of fish bones[167] Rat-bite fever with complicating subacute bacterial endocarditis may be caused either by the Streptobacillus moniliformis[1, 2, 75] or by the Spirillum minus[84] Rarely bacilli of the subtilis group clostridia Micrococcus tetragenus Diplococcus mucosus Diplococcus crassus B necrophorus (B fusiformis), Doederlein s bacillus or C diphtheriae[18] may cause subacute bacterial endocarditis Hoeprich and Chernoff[85] reported a case of subacute bacterial endocarditis due to the gram-positive bacillus Listeria *monocytogenes* cured by 4 million units of penicillin and 2 gm of streptomycin daily for about four weeks The tubercle bacillus attacks the endocardium rarely but only as part of a generalized miliary tuberculosis or by extension of pericardial and myocardial tuberculosis

Mixed Infections and Reinfections

Mixed infections occur occasionally and may present difficulties in the interpretation and treatment of a given case[144] I have seen combined infections with Streptococcus viridans and the pneumococcus S viridans and Staphylococcus aureus S viridans and diphtheroids the Staphylococcus aureus and the enterococcus Staphylococcus albus and enterococcu Combined infection with S viridans and H parainfluenzae was reported by Olinger[142] The combination of Brucella bacteremia and Streptococcus viridans endocarditis was reported by Quinn and Brown[157] but the course and findings suggest that Streptococcus viridans may have been only a transient invader of the blood stream One of the organisms may be rapidly eradicated by antibiotic therapy but the disease may continue because of persistence of the other causative organism which requires larger dosage more prolonged treatment or streptomycin or other antibiotics instead of penicillin

There are already numerous instances of reinfection causing subacute bacterial endocarditis following cure with penicillin That the new attack is due to a fresh infection is certain when the latter attack is caused by a different organism from the one responsible for the former However reinfection with the same species of organism rather than a relapse may be assumed as probable if three months elapse after all clinical and laboratory evidence of the infection has disappeared The more conservatives demand a free interval of a year In one patient I have seen a bacterial endocarditis due to Staphylococcus aureus cured by penicillin a second attack one year later due to a microaerophilic streptococcus likewise cured by penicillin and a third attack six months later due to a Streptococcus viridans from which he also recovered

PREDISPOSING FACTORS

Previous Valvular Disease

Rheumatic Cardiovalvular Disease Subacute bacterial endocarditis usually involves a heart with an acquired valvular defect due to rheumatic fever Even before 1900 Kelynack[105] had found bacterial endocarditis often associated with preexisting valvular disease, and shortly afterward Glynn[66] emphasized this relationship in a study of 61 cases of bacterial endo-

in 60 per cent In my postmortem observations, evidence of rheumatic heart disease was present in 79 per cent of 100 consecutive cases of subacute bacterial endocarditis A similar incidence of underlying rheumatic cardiovalvular disease was noted by Seabury [174] while Christian [3] recorded 134 instances (89 3 per cent) of rheumatic heart disease in 150 consecutive cases of subacute bacterial endocarditis Subacute bacterial endocarditis may develop in hearts with active or inactive rheumatic disease Aschoff bodies have been encountered in about 40 per cent of the hearts with subacute bacterial endocarditis[191, 7] but a similar incidence of Aschoff bodies may be observed in chronic rheumatic heart disease without bacterial endocarditis Bacterial endocarditis occurs less frequently with very severe mitral stenosis than in cases with milder mitral valvular disease or aortic insufficiency [187]

Bicuspid Aortic Valve Of special interest is the association of subacute bacterial endocarditis with bicuspid aortic valves Lewis and Grant[117] noted that more than 23 per cent of males who reached adult life with this abnormality died of subacute bacterial endocarditis Furthermore, in a consecutive series of 31 cases of subacute bacterial endocarditis a congenital' bicuspid aortic valve was found in 26 per cent However in a subsequent study from the same hospital, Wauchope [90] found that only 6 (11 5 per cent) of 52 cases with aortic bicuspid valves developed subacute bacterial endocarditis and 2 of these 6 had other congenital abnormalities as well Wauchope also observed that there were only 5 instances of bicuspid aortic valves among 95 cases of subacute bacterial endocarditis

While Lewis and Grant[117] considered the bicuspid aortic valve to be a congenital malformation, Gross[71] presented evidence that the majority of bicuspid aortic valves are actually deformed cusps due to healed rheumatic infection Koletsky[111] arrived at a similar conclusion as a result of his studies of 50 bicuspid aortic valves, 40 of which were rheumatic and 10 of congenital origin In 8 of the 50 (16 per cent) there was a superimposed bacterial endocarditis—acute or subacute According to Koletsky, bicuspid aortic valves are encountered in 6 to 12 per cent of cases of bacterial endocarditis

Syphilitic Aortic Valvular Disease Occasionally bacterial endocarditis originates in valves deformed by syphilis [99] In Christian's [3] series of 150 cases of subacute bacterial endocarditis there was 1 instance of syphilitic aortitis and 3 of combined rheumatic and syphilitic cardiovalvular disease Koletsky[112] also stressed the simultaneous presence of rheumatic disease in most instances of combined bacterial endocarditis and syphilitic cardiovascular disease and doubted the significance of syphilis as a predisposing factor The infrequency of bacterial endocarditis in syphilitic aortic insufficiency may be due at least in part to the relative infrequency of syphilitic as compared with rheumatic valvular disease There is also a difference in anatomic lesions, for in syphilis there is neither a true valvulitis nor verrucous alteration to trap bacteria as in rheumatic fever

Congenital Cardiovascular Abnormalities

Congenital cardiovascular anomalies are next in importance to rheumatic deformities in predisposing to subacute bacterial endocarditis Cardiovascular anomalies are present in less than 10 per cent of the latter cases Conversely Gelfman and Levine[60] noted that bacterial endocarditis occurred in 6 5 per cent of all cases of congenital cardiac defects and in 16 5 per cent of those patients who survived the age of two

Of the grosser congenital cardiac lesions the patent ductus arteriosus is most frequently involved in my experience The vegetations produce an endarteritis of the pulmonary artery and of the ductus Some observers have found that the interventricular septal defect is more often complicated by bacterial endocarditis e g, Gelfman and Levine[60] noted bacterial endocarditis in 42 per cent of the cases of ventricular septal defects as compared with 28 6 per cent of the cases of patent ductus However the much higher incidence of the latter anomaly accounts for a significantly greater absolute number of cases of bacterial endocarditis with patent ductus arteriosus. The relation of bacterial endocarditis to bicuspid aortic valves has been discussed Jouve[104] believes that pulmonary stenosis is the congenital cardiac lesion most frequently complicated by bacterial endocarditis this may occur in cases of tetralogy of Fallot or in uncomplicated pulmonic stenosis

Bacterial endocarditis complicates a congenital subaortic stenosis more frequently than recorded figures indicate [199] Bacterial vegetations of the aorta are not uncommon in

cases of congenital coarctation Properly speaking these are instances of subacute bacterial aortitis but the clinical picture and course are essentially identical with that of subacute bacterial endocarditis Subaortic stenosis coarctation and bicuspid aortic valve may all be present in the same case In cases of interatrial septal defects there is a striking rarity of subacute bacterial endocarditis

Arteriovenous Aneurysm

Rarely a traumatic arteriovenous aneurysm is complicated by a bacterial endarteritis similar to that complicating a patent ductus arteriosus [117] The bacterial endarteritis usually is further complicated by a bacterial endocarditis if antibiotic or surgical treatment (p 695) is not instituted early

Operative Procedures—Dental Extraction and Tonsillectomy

It has been repeatedly noted that subacute bacterial endocarditis develops following the extraction of a tooth or the removal of tonsils especially in subjects with rheumatic or congenital cardiac defects [94, 134] The Streptococcus viridans is the common organism found in infected tonsils and dental apical abscesses and may be thrust into the blood stream by the operative procedure Okell and Elliott[141] observed a transient bacteremia (preponderantly Streptococcus viridans) following dental extraction in 72 per cent of patients with septic mouths and in 32 per cent of subjects without obvious infection of the oral cavity Similar observations have been made by others [152] Burket and Burn [9] demonstrated the dental origin of the bacteremia by implanting a non pathogen (Serratia marcescens) about the teeth and recovering it from the blood stream following dental extraction Transient bacteremias have also been observed following tonsillectomy [45] Such transitory bacteremias are rarely significant in the normal individual but in persons with cardiovascular abnormalities the microorganisms may localize about the endocardial defects and set up a bacterial endocarditis It is also probable that less decisive traumata than extraction of teeth or tonsillectomy e g brushing or filling of teeth chewing etc may initiate transient bacteremias especially in patients with dental or gingival infection

Among operative procedures those on the genitourinary tract (cystotomy prostatectomy transurethral resection and even cystoscopy and catheterization) have in my experience been responsible for inducing not only transient bacterial invasion of the blood stream but also subacute bacterial endocarditis The causative organism in these cases is usually the enterococcus the Friedlander bacillus (Klebsiella pneumoniae) Escherichia coli Pseudomonas aeruginosa (B pyocyaneus) or rarely B proteus Induced abortions have several times in my experience accounted for the development of acute or subacute bacterial endocarditis Anaerobic streptococci enterococci and Staphylococcus aureus have been the usual causative organisms but in one case there was a mixed infection with enterococcus and Staphylococcus aureus The staphylococcus and occasionally other bacteria have been responsible for endocarditis following mitral commissurotomy [3] and other cardiovascular operations

The possibility that infections of the intestinal tract especially those associated with diarrhea, or even drastic purgation or enemata may precipitate bacteremia and bacterial endocarditis is not far fetched Enterococcic infections are particularly likely to have their portal of entry in the intestine

Respiratory Infections

Because the Streptococcus viridans and Hemophilus influenzae organisms the common causative agents of subacute bacterial endocarditis, are frequent normal inhabitants of the upper respiratory tract their invasion of the blood stream and implantation on deformed valves may be facilitated during an upper respiratory infection Infections of the upper respiratory tract together with dental infections and tonsillectomy have been indicted as precipitating factors in over 70 per cent of cases of subacute bacterial endocarditis [134, 192] In some instances however the patient reports the disease to have followed a cold' or the grippe when actually the so-called grippal episode was itself the manifestation of bacterial endocarditis

Pregnancy and Puerperium

Bacterial endocarditis may have its onset during pregnancy or shortly after childbirth [34] During pregnancy the relationship is probably coincidental However childbirth itself may be associated with transient bacteremia especially when there is pelvic inflammatory disease In patients cured of bacterial endocarditis before or during pregnancy, the remainder of pregnancy and childbirth followed uneventfully [149]

Myocardial Infarction

Bacterial endocarditis has occurred very rarely in patients following myocardial infarction, superimposed on a concomitant aortic insufficiency, it has developed on a mitral valve made insufficient by rupture of an infarcted papillary muscle and in a mural thrombus which became infected

Age and Sex

The highest incidence is in the third and fourth decades, and also commonly in the second But bacterial endocarditis may occur at almost any age from early childhood to late in life I have seen it in a man of 74 It is perhaps wise to stress the occurrence of bacterial endocarditis in the elderly because the disease may be atypical and usually overlooked in these individuals[198] Many cases have been reported in children but rarely under the age of 5

There is a somewhat higher incidence in males than in females[1 2 11 174]

PATHOGENESIS

Portal of Infection

The development of subacute bacterial endocarditis is dependent on the entrance of microorganisms into the blood stream Because the common causative organisms are inhabitants of the mouth and upper respiratory tract, the portal of entry is believed to be located in infected foci about the teeth tonsils nasopharynx and oropharynx The demonstration of transient bacteremias following dental extractions and tonsillectomy and the clinical observations that bacterial endocarditis often follows extraction of teeth or tonsillectomy support this localization of the portal of entry The portal of entry may also be located in the urinary, genital intestinal or biliary tract in cases of enterococcus (Strepto*coccus fecalis) endocarditis*

Experimental Endocarditis

Bacterial endocarditis has been produced experimentally by the intravenous injection of a variety of organisms The disease may be induced by repeated intravenous injection of non hemolytic streptococci from cases of bacterial endocarditis or other human sources[1 1 29] But as a rule experimental bacterial endocarditis is produced more readily if a cardiac valve is damaged first[83] if the bacteria are injected together with coarse particles which aid valvular implantation, or if casein pituitrin or other substances are first injected, presumably to modify the immunologic response or alter the surface of the valve in such a manner as to promote bacterial adhesion[139]

Bacterial endocarditis has also been produced by the preliminary creation of a large arteriovenous fistula in dogs, followed after an interval by the intravenous injection of small numbers of beta hemolytic streptococci[125 158] Rats exposed to a simulated altitude of 25,000 feet develop valvular lesions and on subsequent intravenous injections of nonhemolytic streptococci develop bacterial endocarditis[83] This may be due to predisposition caused by anoxia and polycythemia

These experimental data correspond to clinical observations that previous valvular damage and bacteremia are the two main factors *responsible for the development of* subacute bacterial endocarditis but that the former is not essential The frequency with which rheumatic cardiovalvular disease precedes bacterial endocarditis suggests that immunologic factors may be of some significance but the bacterial endocarditis may develop on normal valves or in hearts with congenital anomalies in which immunologic alterations are not apparently concerned

Method of Implantation of Bacteria on Valves

It is probable that the bacteremia which initiates bacterial endocarditis is usually of very brief duration and occurs either in the course of ordinary physiologic activities as a result of infections of the oral cavity upper respiratory, intestinal or genitourinary tracts or because of operative procedures in these regions Occasionally the responsible bacteremia is more persistent and a part of a general infection (undulant fever, gonococcemia or meningococcemia)

The circulating bacteria are implanted on valves, mural *endocardium* or vascular intima by way of the general blood stream Platelet thrombi on previously damaged valves or recent valvular vegetations aid in the localization of the infection[69 72] The development of a fibrin wall may provide a medium of growth at the same time that *it protects* against bactericidal substances

But the localization and implantation of bacteria are determined chiefly by mechanical factors of impact and perhaps contact[47 2] The bacteria appear to settle and multiply wherever they are sprayed *forcefully* on a receptive area This is often determined by changes in

pressure dynamics and stream flow induced by valvular stenoses and insufficiencies or by cardiovascular shunts In hearts with a patent ventricular septum the endocarditis appears on the endocardium of the pulmonary conus of the right ventricle opposite the septal defect through which a stream of bacteria laden blood is sprayed against the opposite wall In cases of patent ductus the endarteritis begins in the pulmonary artery as if it were forcibly sprayed there through the open ductus In these instances as in valves altered by rheumatic fever tension changes in the mural endocardium or vascular intima may favor bacterial implantation However implantation may occur on apparently normal valvular or mural endocardium but this is more likely in the acute bacterial forms of endocarditis due to more virulent organisms and more persistent bacteremias

PATHOLOGY

THE HEART

Valves and Vegetations

The most striking feature is the presence of *vegetations* on the valves and on the parietal endocardium These may be discrete like rheumatic verrucae but are usually larger They may also be flat and granular or occasionally exuberant fungating or cauliflower vegetations Rarely the latter are large enough to occlude a valvular orifice The two important characteristics of these vegetations are (a) the presence of bacteria which are constantly swept into the blood stream and which are responsible for the fever toxemia and bacteremia of the disease and (b) their friability which accounts for the fragmentation of particles which are disseminated as embolic bacterial masses

Microscopically the vegetations have a broad base of altered degenerated valvular substance with blood platelet thrombi accumulations of bacterial masses all overlaid by a fibrin and erythrocyte coating Sometimes the vegetation has a characteristic appearance resembling necrotic liver cords [7] Polymorphonuclear leukocytes which abound in acute bacterial vegetations are few or absent in the subacute cases The underlying valvular cusp is the site of a diffuse destructive process with an inflammatory exudate of lymphocytes, mononuclear cells and some polymorphonuclear leukocytes Sometimes there is a striking infiltration of large mononuclear cells consisting of histiocytes and fibroblasts

Localization of Vegetations

The vegetations are situated predominantly on the left side of the heart except when there is a congenital communication between the two sides The vegetations are localized chiefly to the valvular leaflets the mitral being affected in about 80 per cent of the cases the aortic in 60 per cent both in 40 per cent The aortic valve is most likely to be involved in cases of primary bacterial endocarditis i e without antecedent disease The pulmonic valve is occasionally affected perhaps with more than casual frequency in the gonococcal cases The tricuspid valve may be affected simultaneously with the aortic or mitral[1-3] but it seems to have been the site of predilection in cases of Staphylococcus albus and aureus endocarditis induced by intravenous injection of contaminated heroin In one case of interatrial defect which I observed the tricuspid valve was the only one infected with bacterial vegetations

The vegetations may also be situated on the chordae tendineae or on the mural endocardium especially of the left atrium or left ventricle and occasionally on the interventricular septum or pulmonary conus of the right ventricle or on vascular intima Bacterial involvement of the chordae may lead to necrosis and rupture and their loose ends may be seen dangling unattached The aortic valvular vegetations frequently spread by contiguity along the ventricular endocardium and produce moth-eaten bacterial lesions on the ventricular surface of the anterior mitral cusp They may also extend to the distal surfaces of the aortic cusps and involve the sinuses of Valsalva and the adjacent aortic intima In the left atrium bacterial vegetations may produce a characteristic nodular plaque-like lesion with a coarse sharkskin appearance [7] often superimposed on a previous rheumatic atrial lesion

Local Complications of Bacterial Vegetations

The destructive effect of the bacterial vegetative lesions leads to *complications* including *mycotic aneurysms perforations of valve cusps rupture of chordae tendineae perforations of interventricular septa or sinus of Valsalva*

Necrosis of valvular substance may lead to local ulceration aneurysmal pouches or occasionally to perforation of cusps [170] Bacterial endocarditis may increase the anatomic de

formity and functional impairment previously present or initiate a valvular insufficiency or rarely a stenosis. Extension of the bacterial infection to the septum may involve the conduction system. I have several times observed ulceration of a mycotic aneurysm at the base of the aortic valve extend into the pericardial space between the roots of the aorta and pulmonary artery and produce a clinically apparent purulent pericarditis. Bacterial necrosis of the sinus of Valsalva may lead to aneurysm formation and occasionally to perforation into the right atrium or right ventricle with characteristic clinical symptoms and signs of a communication between two vessels or chambers of different pressures (p 773). Rarely aortic and very rarely tricuspid vegetations may burrow into the subjacent myocardium and produce a perforation of the interventricular septum or septum fibrosum.

Healing of Vegetations

Healing of vegetations of subacute bacterial endocarditis were noted by Harbitz,[78] Osler[145] and others, and carefully studied by Libman[1 0] and by Gross and Fried.[72] In recent years healed lesions have been noted at various periods following bacterial sterilization by means of penicillin, when death resulted from some cause other than persistent infection.[164, 136, 99, 29] Healing begins early in the deeper parts of the vegetation and is characterized by disappearance of the valvular inflammatory reaction and bacteria, marked capillarization of the subjacent valve and a fibroblastic reaction. The dilated capillaries may communicate with the cardiac chambers and produce a characteristic "spongy" lesion consisting of wide anastomosing cavernous channels. The fibroblastic reaction leads to partial or complete organization and hyalinization of the vegetations often with calcification. If bacteria are present they lose their staining quality and cannot be cultured. Eventually the small remnant of the hyalinized and fibrotic vegetation becomes covered with an endothelial layer. In the penicillin-treated cases complete healing occurs in about three months after clinical control of the infection.

Myocardial Lesions

Interest in myocardial lesions has been heightened because of the frequency of cardiac failure despite control of the bacterial infection by antibiotics.

Two types of myocardial lesions may be noted:[33, 17, 151] (a) vascular lesions consisting of bacterial embolization of arterioles and capillaries, necrosis of the walls of these small vessels and surrounding inflammatory reactions, (b) extravascular lesions characterized chiefly by minute infarctions due to the above vascular lesions and foci of polymorphonuclear leukocytes or mononuclear cells. Perivascular fibrosis and organization of minute infarcts are common.[16] Small foreign body granulomata surrounding a central deposit of calcium (embolic) have been described in fatal cases treated with sulfonamides and penicillin.[169] Suppurative lesions are uncommon but occur in the cases due to pyogenic microorganisms. The so-called Bracht-Wachter[16] lesions are focal collections of lymphocytic and mononuclear cells. They are not characteristic and are of dubious significance. Occasionally bacterial embolization involves the larger coronary arteries[146, 21] and may produce gross myocardial infarction[196] or sudden death. Not infrequently there are Aschoff bodies and other lesions due to coexisting rheumatic myocarditis.

Pericardial Lesions

Pericardial involvement is uncommon in subacute bacterial endocarditis but there may be lesions of a previous or concomitant *rheumatic* inflammation. Occasionally a diffuse pericarditis is due to an associated pneumonia or complicating uremia. A specific gross suppurative pericarditis may, however, be due to extension of the bacterial infection from an aortic valve and sinus of Valsalva to the pericardial wedge between the aorta and pulmonary artery. In one such case I observed *500 cc* of serosanguineous pericardial fluid.

KIDNEY

The renal lesions are of three types: (1) focal "embolic" glomerulonephritis, (2) diffuse glomerulonephritis and (3) infarcts. There is evidence that penicillin therapy has diminished the incidence of renal lesions in bacterial endocarditis, especially of diffuse glomerulonephritis.[177] Grossly the kidney may present diffuse petechial hemorrhages which produce the so called "flea bitten" appearance and depressed, yellowish sharply demarcated areas of infarction.

1 The *focal embolic glomerulonephritis* (the Lohlein Baehr) lesion was first described by Lohlein[1 9] and studied in detail by Baehr[4] who observed it in 23 of 25 cases of bacterial endocarditis due to the *Streptococcus viridans*

It may also occur in cases due to the H influenzae

Microscopically the feature of the lesion is the necrosis of only a portion of glomerular vessel wall and the presence of a fibrinoid plug in the lumen of the corresponding glomerular branch [24] The lesion has generally been regarded as embolic but it is more probable that local vascular inflammation and closure are responsible [25] Since bacteria are not found in the lesions they may represent an immunologic reaction to the bacterial infection The swollen, necrotic portion of glomerulus becomes granular, undergoes hyalinization and organization and becomes adherent to the parietal layer of Bowman s capsule or subjacent interstitial tissue, its sides being covered by a reflection of the epithelium from Bowman s capsule A characteristic pyramidal or wedge-shaped lesion is produced Few or many glomeruli may be involved When numerous glomeruli are involved renal insufficiency results In the bacteria free stage only the healed hyaline (fibrous) form of this lesion is observed [4]

2 *Acute or subacute glomerulonephritis* was formerly described as infrequent in the active stage of Streptococcus viridans endocarditis but was encountered commonly in the cases due to the gonococcus or pyogenic organisms However according to Christian[23] a diffuse proliferative glomerulonephritis was encountered in 80 per cent of the kidneys of 61 cases of subacute bacterial endocarditis which he studied A diffuse glomerulonephritis was common in the bacteria free cases described by Libman[1 3] and in cases of healing by penicillin [29]

3 *Infarcts* occur in about 90 per cent of untreated cases but are seen uncommonly when treatment is instituted relatively early One or more infarcts may be present They are generally bland but in the cases due to the enterococcus purulent infarcts have been noted

SPLEEN

The spleen is almost invariably enlarged, sometimes remarkably so The usual weight is between 200 and 500 gm but I have seen spleens over 600 gm independent of other splenic disease The spleen contains one or more anemic infarcts in 40 to 60 per cent of the cases Suppuration occurs rarely A perisplenitis with adhesion to the diaphragm may be associated Rupture of the spleen has been reported [107] On section the spleen presents the picture of a subacute or chronic splenic tumor The malpighian bodies are frequently enlarged and prominent and in the bacteria free stage may be visible as grayish punctate dots which give the spleen a characteristic aspect

Microscopically there is hyperplasia of the lymphoid follicles with conspicuous secondary follicles There is a considerable proliferation of the reticulum cells and occasionally of the sinus endothelium [110] In the red pulp the granulocytes are overshadowed by lymphocytes plasma cells and free histiocytes showing phagocytosis The intersinusoidal cords of Billroth are widened There may be foci of necrosis of the reticulum or of the center of the follicles as well as mononuclear cellular collections Focal or diffuse fibrosis of the fibrillar reticulum probably represents a healing or late stage of the disease Jouve[107] has also described a sclerosis of the lymphoid follicles and splenic tissues

CENTRAL NERVOUS SYSTEM

Lesions of the brain are frequent and widespread in uncontrolled cases [36] There is often a diffuse meningoencephalitis due to disseminated bacterial embolization of arterioles and capillaries [109 110] Local closure may also occur secondary to an arteritis and intimal proliferation with or without thrombosis There is a diffuse or perivascular proliferation of micro- and macroglial cells and of astrocytes without polymorphonuclear cells or lymphocytes Ganglion cells undergo ischemic degeneration The meningoencephalitis may involve the cerebrum cerebellum or cerebral ganglia Occasionally the spinal cord is involved in a similar process and a funicular myelosis has been described

Embolic lesions of the large cerebral arteries are common in fatal cases Bacterial emboli lead to mycotic aneurysms and thrombosis Cerebral intraventricular or subarachnoid hemorrhage may result from rupture of a mycotic aneurysm while encephalomalacia is a consequence of vascular (embolic) occlusion Occasionally small or large cerebral abscesses are encountered probably due to autolysis with secondary polymorphonuclear invasion of the infarcted areas

LIVER

The liver is considerably enlarged and engorged This is due essentially to chronic pas

sive congestion which is seen in most fatal cases In addition there is fatty infiltration and focal necrosis There may be enlargement and desquamation of the Kupffer cells and focal accumulations of histiocytes [7]

LUNGS

Congestion, pulmonary emboli and infarctions and bronchopneumonia may be encountered Less often there are pleural effusions or hemorrhages

BONE MARROW

There may be considerable regeneration in both the active and bacteria free stages

ARTERIAL LESIONS MYCOTIC ANEURYSMS

Arterial lesions consist of embolization or arteritis Bacterial emboli affect the large or small vessels of the brain, the extremities, the spleen the kidney, the lungs, or of the hepatic or gastrointestinal tracts Embolization of the lung may arise independently from venous thrombi in the lower extremities or from bacterial vegetations on the right side of the heart in congenital cardiac lesions or endocarditis of the tricuspid or pulmonic valves Vascular occlusion results in infarction or gangrene

Bacterial embolization also results in destruction of portions of a vessel wall with weakening of its structure and the formation of so called mycotic (bacterial) aneurysms [162] Most probably necrosis of the wall is secondary to infected emboli which arrive by way of the vasa vasorum and not by direct implantation on the intimal surface with secondary growth and extension

Many of the cutaneous lesions formerly considered the result of vascular embolization, are probably due to local inflammatory changes in the walls of capillaries or arterioles, possibly immunologic responses to the infection Thus the Osler node is essentially a vascular lesion in which one or more arterioles are occluded by intense intimal proliferation [131, 113, 23] Neighboring capillaries and arterioles show endothelial proliferation and desquamation, thrombosis or necrosis There is a perivascular inflammation of polymorphonuclear leukocytes and histiocytes and a diffuse cellular infiltration in the dermis and about the sebaceous glands and nerve endings The white-centered petechiae in the skin and the so-called focal "embolic glomerular lesion may also be due to local vascular inflammation rather than to embolization

CLINICAL FEATURES

MODE OF ONSET AND GENERAL COURSE

The onset is usually insidious Often the patient is known to have a rheumatic or congenital cardiac defect from which he has suffered little or not at all Most frequently there is only fatigability, weakness or lassitude, anorexia and low grade fever Moderate frontal headache often accompanies the fever A considerable loss of weight may be noted Fever, associated with joint and muscle pains is frequently suggestive of an attack of "grippe" Or symptoms of the disease develop insidiously after a tooth extraction, tonsillectomy, cystoscopy, genitourinary operation or childbirth Symptoms of heart failure are occasionally the first evidences of the disease Almost any other symptom of the disease may be the first manifestation, but urinary, cerebral and digestive disturbances may be particularly mentioned

Occasionally the onset is acute, owing generally to an embolic thrust in a cerebral, abdominal or peripheral vessel Thus hemiplegias local paralysis of an extremity, blindness due to embolism of the retinal vessel sharp pain in the abdomen or loin due to splenic or renal infarction may suddenly reveal the presence of a bacterial endocarditis in an apparently well person I recently observed a 60 year old woman in whom the first symptom was aphasia without paralysis, which developed while she was in the subway on her way to work Because of her age the aphasia was thought to be due to atherosclerotic cerebral thrombosis and she was admitted to the neurologic service The true nature of the disease was recognized upon the discovery of mitral stenosis and low grade fever *Toone*,[131] Seabury[174] and others have called attention to the relative frequency with which patients with subacute bacterial endocarditis are admitted to the neurologic service of a hospital because of cerebral manifestations at the onset

The onset may also occur acutely with chills and high fever This is particularly frequent in the acute cases due to the *Streptococcus hemolyticus* staphylococcus, pneumococcus *E coli*, and similar pyogenic organisms

The further course of the disease is variable and depends essentially on the speed with

which adequate treatment is instituted or serious embolic complications occur In the absence of such treatment or complications the patient runs either a prolonged subfebrile course with progressive weakness and anemia or a rapid acute course Eventually if there is no treatment or if treatment is unsuccessful death results from cardiac failure a cerebral accident uremia or an intercurrent infection The duration is less than a month or two in the acute cases due to pyogenic organisms or occasionally in the subacute disease when the course is abbreviated by an embolic lesion with resulting cerebral or subarachnoid hemorrhage Usually there are repeated evidences of embolization and numerous organs are involved before the fatal complication occurs During this period the patient may have periods of apyrexia and even of tolerable comfort

SYMPTOMS AND SIGNS

These may be classified into three groups (1) general or toxemic (2) embolic and vascular (3) cardiac With early diagnosis and treatment, very few of these symptoms should develop

1 General or Toxemic Symptoms

The general symptoms result from the toxemia of the bacterial infection Fever is the most constant It may be continuous remittent intermittent or completely irregular As a rule the daily temperature peaks range between 101 and 103° Periods of subfebrile temperature for weeks at a time are occasionally observed in the subacute cases Periods of apyrexia may be noted occasionally in patients with renal insufficiency and rarely in others Shaking chills occur in the acute cases occasionally There may be profuse sweats In patients who suffer chills the temperature is likely to be higher than that described above It may reach 104 to 105 F with sharp septic swings A daily double-peaked rise in the temperature curve (double quotidian type of fever) has been described as characteristic of meningococcic endocarditis [51] but also of gonococcic endocarditis [III] Headache is common Often in uncomplicated cases frontal headaches associated with an afternoon rise in temperature are the only symptoms

Progressive anemia is a characteristic feature unless effective treatment is instituted early Certain other symptoms are due partly to the fever and toxemia and partly to the anemia These include weakness, breathlessness and easy fatigability

2 Embolic and Vascular Manifestations

The embolic symptoms are the specific evidences of this disease Seabury's[174] review of the clinical history of 165 cases of subacute bacterial endocarditis disclosed that embolization occurred at the onset in 6 7 per cent But as a rule embolization occurs later when the disease is fairly advanced Only closures and aneurysms of large vessel with resulting infarctions of organs paralysis of extremities or cerebral accidents can be definitely included under this heading Other symptoms whose embolic nature is not certain are very helpful in the diagnosis and include white-centered petechiae and Osler nodes The latter may produce painful fingers or toes which are sometimes the earliest symptom or chief complaint

3 Cardiac Signs

The cardiac signs are essentially those indicating a valvular lesion or a congenital cardiovascular deformity Usually there are murmurs and other signs of mitral stenosis or aortic insufficiency due to known rheumatic infection There may be signs of a patent ductus arteriosus a ventricular septal defect subaortic stenosis or a coarctation of the aorta Sometimes there are changes in the character and sites of these murmurs or new murmurs appear during observation of the patient Occasionally a new rasping murmur is observed with dramatic suddenness due to a rupture of a chorda tendinea or perforation of a valve cusp I have repeatedly observed the development of the characteristic signs of aortic insufficiency in persons with subacute bacterial endocarditis in whom the valves were previously normal A murmur is sometimes absent when the endocarditis is confined to the right side of the heart and involves a previously normal valve [6]

SYMPTOMS OF INDIVIDUAL ORGAN SYSTEMS

Skin and Mucous Membranes

Pallor is almost invariably obvious A characteristic appearance of the patient is often produced by a muddy pallor to which Libman has applied the descriptive term café au lait'

The most frequent skin lesions are *petechiae* those with so-called white centers (actually yellowish gray) being especially significant The white centers are not raised in the subacute cases as they are in some of the acute

bacterial cases The petechiae are most frequently and best observed in the conjunctiva, especially of the lower lid, in the fundus, in the skin about the clavicles, and in the oral mucosa particularly on the soft and hard palates In ambulant patients, petechiae may also be found in the lower extremities A characteristic feature is the occurrence of the petechiae in crops which disappear after several days and recur at a later period However isolated petechiae are also common

Even more specific are tender cutaneous lesions termed *Osler nodes*[115] These are small raised swollen areas about the size of a pea but they may be larger or as small as a pinhead Characteristically they have a bluish tint but they may be pink or red, and rarely possess a blanched center Most commonly they occur in the pads of the fingers or toes, in the thenar or hypothenar eminences or the soles of the feet and rarely on the sides of the fingers or on the webs between the toes[1] The essential feature of these lesions is that they are always tender. The patient may note their sudden onset because of the pain produced In fact painful fingers due to Osler nodes may be one of the chief complaints The Osler node usually lasts one to several days but may disappear in a few hours According to Libman[10] it is pathognomonic of subacute bacterial endocarditis

The Osler node must be distinguished from the *Janeway lesion*,[93] which is more characteristic of acute bacterial endocarditis but is occasionally seen in subacute bacterial endocarditis This is a small erythematous or hemorrhagic lesion which is sometimes raised and nodular but never painful In subacute bacterial endocarditis it is more apt to appear as an erythematous lesion without a hemorrhagic or purple center It usually occurs in the palms of the hands or the soles of the feet

A rather characteristic lesion of the fingers which may be embolic or toxic, is the so called splinter hemorrhage[11] These are vertical hemorrhagic streaks in the skin under the nails

Pustular lesions may occur in staphylococcus or gonococcus endocarditis or endocarditis due to other pyogenic microorganisms Crops of macules and papules have been described in meningococcal and gonococcal endocarditis Occasionally there are large, extensive purpuric lesions which may or may not be associated with thrombocytopenia, prolonged bleeding time and other typical blood findings of purpura hemorrhagica

Kidneys

Hematuria, usually microscopic but occasionally gross, is commonly observed at some stage of the disease As microscopic hematuria is very significant for diagnosis in a doubtful case and as only a few red blood cells may be present in casual specimens careful and repeated examinations should be made on centrifuged specimens of urine Albuminuria is almost invariable, even when no glomerular lesions or infarcts are found

Renal insufficiency occurs infrequently since effective therapy is available Usually renal insufficiency is denoted by a slight or moderate azotemia (urea nitrogen 25 to 75 mg/100 cc) and a fixation of urinary specific gravity to 1 010 by the concentration test Even in the presence of renal insufficiency the blood pressure remains low Renal insufficiency may be due to extensive glomerular embolization or to subacute diffuse glomerulonephritis A nephrotic syndrome occurs rarely

Gross infarctions may be associated with pain as well as with hematuria and albuminuria The pain may be located in the loin It may radiate anteriorly and into the groin as a result of the passage of blood clots along the ureter Tenesmus and frequency of urination also occur

Spleen

A large spleen is clinically palpable in about two thirds of patients But even a large spleen may not be palpable either because the enlargement is very moderate or because the spleen is fixed to the diaphragm by adhesions Splenic infarction may be characterized by sharp sudden pain in the left hypochondrium or the left lower axilla which may radiate to the left shoulder or precordium There may be local tenderness and rigidity over the splenic region, and occasionally a rub is heard so that a pleurisy is diagnosed In rare cases the infarcted spleen may rupture and lead to peritonitis, or peritoneal hemorrhage and sudden death Sudden death may also result from rupture of a bacterial aneurysm of the splenic artery

Heart

The presence of old cardiac murmurs and the development of new ones due to the bacterial infection have been mentioned However, there may be no cardiac murmurs throughout the course of the disease

Cardiac failure is relatively rare at the time bacterial endocarditis begins, i.e., subacute bacterial endocarditis usually attacks the well compensated cardiac patient. On the other hand, congestive heart failure occurs commonly after the development of the bacterial infection. Heart failure is due to destruction of valve tissue, especially with the production of aortic insufficiency, and to myocardial damage caused by bacterial myocarditis and embolic vascular lesions.

Cardiac failure has become the most important complication of bacterial endocarditis since the advent of antibacterial treatment with penicillin. For heart failure is often responsible for death even when the bacterial infection is eradicated.[19, 93, 105]

Disturbances of conduction are uncommon in contrast with their frequency in rheumatic fever[166, 37] but they have been reported to occur frequently in the cases due to pyogenic organisms and especially in brucella endocarditis. Patients with established atrial fibrillation are not likely to develop the disease.[1, 197] However, exceptions do occur. In the cases of prolonged duration which have become bacteria free, and in those in which congestive heart failure develops, atrial fibrillation is as common as in uncomplicated chronic rheumatic valvular disease. The most frequent disturbance in rhythm is a prolongation of the atrioventricular conduction (P-R interval 0.21 to 0.36 second), which occurs in about 15 per cent of the cases. Rarely there is widening and notching of the QRS complex. Complete heart block and bundle branch block may be due to the pressure of a bacterial aneurysm of the sinus of Valsalva on the interventricular septum. *It has been noted particularly in cases* of brucella endocarditis (p. 876). In one such case which I observed at autopsy there was partial heart block ending fatally with Adams-Stokes syndrome due to complete heart block. Heart block and Adams-Stokes syndrome in bacterial endocarditis have disappeared following penicillin therapy.[205]

A *pericardial rub* is rarely heard in subacute *bacterial endocarditis, but it may be present if* there is uremia, or rupture or extension of a mycotic aneurysm into the pericardium.

Coronary occlusion may occur as a result of bacterial emboli from endocardial vegetations.[146] In two such cases which I observed recently the lesion was found post mortem but there were no obvious clinical manifestations. Such emboli may be responsible for sudden death or rarely for myocardial infarction.[196]

Central Nervous System

Cerebral symptoms are a prominent feature of the disease.[166] They may occur at the onset or at any subsequent stage of the disease. The symptoms may resemble those of meningitis or encephalitis.[131] Meningitis is more common in the acute (especially pneumococcal endocarditis) than in the subacute cases. Paralyses are common. Usually the symptoms result from embolic occlusion of a large cerebral vessel.[139] Rupture of an embolic aneurysm not infrequently causes a subarachnoid hemorrhage or fatal hemorrhage into the brain substance or intraventricular spaces.

Encephalopathies may dominate the clinical picture. Usually they are associated with evidences of a meningeal reaction. There may be delirium, somnolence or stupor. When there are blurred vision, vertigo, diplopia, salivation, ocular paralyses, masked facies and muscular twitchings, the picture resembles an encephalitis. Paralyses of the upper motor neurone type are not uncommon. Clinically they appear as a crossed hemiplegia or a monoplegia with or without aphasia. They are caused by a bacterial embolus to a branch of the middle cerebral artery. Flaccid paralyses occur rarely, perhaps as a result of a funicular myelitis. The clinical picture may resemble that of poliomyelitis.

Respiratory Tract

Cough, chest pain, dyspnea and bloody expectoration may be due to pulmonary embolism. This is especially common in cases of bacterial endocarditis with vegetations on the *tricuspid valve, in right-sided bacterial endo*carditis associated with interventricular septal defect and in bacterial pulmonary endarteritis complicating patent ductus arteriosus.[150] Pulmonary emboli may also be secondary to venous thrombi in the lower extremities. Occasionally cough and expectoration result from a complicating bronchopneumonia. Pulmonary symptoms may also be due to left *heart failure*.

Extremities

Clubbing of the fingers is eventually present in about two thirds of the fatal cases in my experience. Cotton[30] first called attention to this symptom, having found that of 63 cardiac patients with this abnormality 44 had definite evidence of bacterial endocarditis. Blumer[11]

noted clubbed fingers in 18 of 48 cases Clubbing of the toes is also frequent

Joint pains are not uncommon or there may be less localized pain in the extremities Pain in the fingers, due to Osler nodes or a subungual hemorrhage, has been mentioned Arthralgias are especially common in the cases of endocarditis due to brucella or meningococcus and arthritis is common in subacute gonococcal endocarditis

Cases of ball valve thrombus occluding the mitral stenosis with consequent bluish necrosis of fingers, toes and tip of the nose have been reported[171]

Sudden pain, loss of function coldness, pallor or cyanosis results from embolization of a large vessel to an extremity Gangrene may follow

Eyes

White-centered petechiae in the conjunctiva are frequent and important for diagnosis They may occur singly or in crops lasting several days Petechiae with and without white centers are also encountered in the retina Often these petechiae have a characteristic boat shaped appearance[41] White-centered retinal hemorrhages may also be observed in cases of leukemia, severe anemia, scurvy and various bacteremias Whitish lesions known as Roth spots are observed both in acute and subacute bacterial endocarditis as well as in other diseases with severe anemia[18]

Optic neuritis and even choked disk have been described as toxic manifestations of the disease[11 37] Usually vision appears unimpaired Kauntze[108] reported 7 cases of subacute bacterial endocarditis in which optic neuritis occurred at the onset or as an early manifestation The neuritis is attributed to vascular occlusion and impairment of blood supply to the nerve The cases with papilledema which I have observed have been associated with meningeal symptoms, a serous meningitis or subarachnoid hemorrhage The finding of optic neuritis in association with other neurologic abnormalities is often responsible for diagnostic error

Sudden blindness may result from embolism of the central retinal artery I have also seen a patient in whom fever and a quadrant defect in the visual field (due to embolism of a retinal arterial branch) were the only manifestations of subacute bacterial endocarditis

The *pathologic changes* in the retina and choroid have been described by Dienst and Gartner[40] They include papillitis edema and cellular infiltrations surrounding the retinal blood vessels and the optic nerve The choroid is especially involved with dense foci of cellular infiltrations, chiefly small round cells

Vessels

Embolization and arteritis are important manifestations Gross embolization with infarctions generally involves the extremities the spleen, the kidneys the lungs and the brain The symptoms have been described in connection with the organs affected Tender swellings of the walls of arteries have been described

Blood

A positive blood culture of the causative organisms is obtained in 80 to 90 per cent of cases This is discussed under etiology and diagnosis

Anemia is a feature of the disease[148] In about 10 per cent of cases the anemia is intense, the hemoglobin falling below 7 gm and the erythrocytes below 2 5 million In patients with purpura I have seen the hemoglobin as low as 3 4 gm The red blood count is usually between 2 5 and 4 million When the infection is controlled by antibiotics there is a rapid increase in hemoglobin and erythrocyte level I observed two cases of hemolytic anemia with positive Coombs test in patients with bacterial endocarditis Whether this was due to the bacterial endocarditis, to drugs administered or to independent factors is uncertain The hemolytic anemia disappeared in one of the patients after prednisone therapy

Leukocytosis is, in my experience, not characteristic unless there is some complication More than one third of the patients I have studied have had a white count under 10,000 Seabury[174] encountered leukocyte counts between 5000 and 10,000 in 53 4 per cent of his cases It is important to emphasize this because many physicians tend to exclude subacute bacterial endocarditis as a diagnostic possibility when the white blood count is not elevated Thayer's[181] series shows that counts above and below 15,000 are equally frequent I have observed that the highest count (20 000 to 40 000) occurred with meningeal and cerebral complications White counts between 15 000 and 25,000 were generally associated with embolism or a concomitant pulmonary infarction When a leukocytosis was present independent of these *conditions*, it was of mild degree (10,000 to 14 000), and the poly

morphonuclear leukocytes were between 65 and 88 per cent with a "shift to the left" in the Schilling hemogram Occasionally there is a leukopenia

There may be a pronounced monocytosis[172] Sometimes the blood contains large phagocytic cells varying in size between 10 and 80 micra[183] These macrophages, histiocytes or endothelial cells as they have been variously termed may dominate the blood picture and are helpful in confirming the diagnosis[185] I do not believe however, that they are pathognomonic or that they are frequently observed

The *blood platelets* are usually normal Not infrequently they are reduced in number and rarely to such low levels that they may produce purpuric manifestations

There is often an elevation of the blood proteins due entirely to an *increase in the serum gamma globulin fraction* The latter accounts for the frequently positive formol gel reaction and for frequently positive cephalin cholesterol flocculation and thymol turbidity tests in subacute bacterial endocarditis Cold precipitable serum globulins (cryoglobulins) were found in 42 of 50 cases of bacterial endocarditis at some time during the period of observation[45]

The *sedimentation rate* of erythrocytes is distinctly accelerated in subacute bacterial endocarditis Increased serum globulin and fibrinogen account for this finding

INDIVIDUAL TYPES OF ENDOCARDITIS

Although the essential features of bacterial endocarditis are similar regardless of the causative microorganism certain features related to some of the individual organisms are worthy of mention

Staphylococcus Endocarditis[41 5]

This type of endocarditis is important because of its increasing frequency and the increasing number of resistant strains of staphylococci Levinson et al[116] reported that of 64 patients with bacterial endocarditis, the staphylococcus was the cause in 18 (28 per cent) In 9 cases the organism was a coagulase positive Staphylococcus aureus and in 9 a Staphylococcus albus Most of the organisms in both groups were highly resistant and there was a 66 per cent mortality with each variety of staphylococcus The fatal cases of staphylococcus endocarditis ran an acute course death usually occurring within one to four weeks Of 13 cases of staphylococcus endocarditis observed between 1949 and 1953 Fisher et al[5] found 42 per cent penicillin resistant, the survival rate was 54 per cent

In acute cases of staphylococcus endocarditis, the disease may follow a furuncle carbuncle abscess or osteomyelitis, especially after traumatization, or it may occur after catheterization or cystoscopy In such cases there are often chills and high fever sweats, prostration petechiae with raised white centers arthritis and a suppurative pneumonia purulent pericarditis or metastatic abscess to the myocardium kidney spleen brain etc Even in the absence of gross infection staphylococci are often present in abundance on the skin and in the nose where they may be harmless but not after introduction into the blood stream of susceptible individuals In a number of cases staphylococci have been introduced into the blood stream by intravenous injection of heroin by addicts[8] Endocarditis in such cases has occurred often in the absence of previous valvular disease and there has been a tendency for localization of the bacterial vegetation to the tricuspid valve

Enterococcus Endocarditis[94 93]

The enterococci formerly responsible for 4 or 5 per cent of the cases of bacterial endocarditis are now responsible for at least 10 to 15 per cent Others have reported the incidence to be about 20 per cent[93] Enterococcus endocarditis is important also because of its high resistance to doses of penicillin which are generally effective in Streptococcus viridans endocarditis Enterococcus endocarditis is most likely to occur following disease or manipulation of the genitourinary tract,[12 60 93] (cystoscopy transurethral resection) occasionally after a septic abortion and rarely in relation to ulcerative lesions of the colon It has followed peripheral abscess and dental extraction, but has occurred also in the absence of overt disease, manipulation or operation Enterococcus endocarditis frequently but in a minority of cases involves previously normal valves Most of the patients are men The onset and course may be acute or subacute more frequently the latter in my experience Suppurative lesions were somewhat more common than in Streptococcus viridans endocarditis but I have not noted this since the vigorous use of antibiotics

Brucella Endocarditis

Relatively few cases of endocarditis due to Brucella organisms have been reported [179, 80, 68] but they deserve comment because of certain purported characteristic features [illegible] As a rule, the patients are males whose occupations bring them in contact with Brucella microorganisms In most cases the aortic valve was involved Of special interest is the frequent occurrence in cases due to Brucella abortus of bacterial aneurysms of the sinus of Valsalva with spread of infection through the aortic wall into the atrial septum, ventricular septum, myocardium or pericardium [illegible] [illegible] The tricuspid valve is involved relatively frequently Disturbances of conduction are common due to septal involvement There is usually a persistent leukopenia In cases due to Brucella melitensis, unlike those due to Brucella abortus, there is usually no previous valvular lesion and rarely aneurysm of the sinus of Valsalva or conduction disturbance Nevertheless, I doubt that Brucella abortus endocarditis represents a distinct entity on the basis of the reported cases, as claimed by Hart et al [80]

Pneumococcus endocarditis is now rare It follows a pneumococcus (lobar) pneumonia or other pneumococcus infections (arthritis, otitis media) The triad of pneumococcus pneumonia, cardiac murmur and meningitis denotes pneumococcus endocarditis, but this is a late stage Undue persistence of fever after pneumonia or recurrence of fever after a brief free interval in a patient with a cardiac murmur should suggest the presence of endocarditis, and blood cultures should be made

Endocarditis due to the Streptobacillus moniliformis or to the Spirillum minus may be suspected when the clinical picture of subacute bacterial endocarditis with multiple arthritis and macular or papular erythema occurs in an individual with a history of rat-bite or of intimate contact with rats In the cases due to Spirillum minus, the incubation period is longer (more than ten days) The local bite lesion is likely to flare up with the development of endocarditis Arthritis is usually absent, and the skin lesions are larger and papular while in the cases due to the streptobacillus the skin lesions are morbilliform and petechial But the clinical picture may be similar in both and both respond to penicillin therapy The causative organisms may be better grown in an atmosphere containing CO_2 than aerobically

Erysipelothrix Endocarditis

A history of handling fish, game or cheese or of polishing fish bones in button making and the presence of an erysipeloid skin lesion together with the clinical picture of bacterial endocarditis, suggest that the latter is due to the erysipelothrix

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The complete diagnosis of subacute bacterial endocarditis is based on the presence of (1) a valvular defect or congenital cardiovascular lesion, denoted by a murmur, (2) a febrile course, (3) embolic phenomena (4) a positive blood culture However, the urgency of early diagnosis and early institution of specific therapy demands an alteration in our criteria for diagnosis

Importance of Early Diagnosis

Despite the availability of curative antibiotics, there is still a substantial mortality of about 25 per cent in cases of bacterial endocarditis In addition, congestive heart failure and, less frequently, cerebral infarction or renal insufficiency, developing during the active bacterial infection cause serious disability and shorten life, even when the infection is cured A study of cases with complications and/or a fatal ending indicated that most of these were due to erroneous or late diagnosis [14] Delay or error in diagnosis was most often due to dependence on development of the full clinical picture before the diagnosis of bacterial endocarditis was seriously considered or rejection of the diagnosis because blood cultures were negative It became apparent that anemia, splenomegaly, clubbing and renal and splenic infarcts were relatively late symptoms Furthermore heart failure cerebral embolism, renal insufficiency and pericarditis were usually irreversible manifestations which were often responsible for fatalities even though adequate antibiotic treatment was instituted An analysis of past cases and subsequent experience have indicated that the highest recovery rate with minimal complication occurs only if the diagnosis is made and treatment instituted within two weeks after the onset of fever, and that accurate diagnosis within this early period is possible on the basis of minimal, early manifestations Hence minimal diagnostic criteria have been set up

Diagnosis By Minimal Criteria

The diagnosis of subacute bacterial endocarditis should be assumed as most probable whenever

a patient with an organic cardiac murmur experiences fever, without apparent cause for more than one week.[63] Often, at this stage a meticulous search will provide strong diagnostic confirmation in the finding of white-centered petechiae in the conjunctiva fundus or palate or Osler nodes A positive blood culture is desirable for definite diagnosis, and as a guide to the choice of antibiotic and dosage in treatment of the disease However, treatment need not await isolation of the causative organism if the diagnosis is based on the above criteria Most common febrile diseases due to infections of the upper respiratory tract or other cause clearly reveal their nature or subside within a week If the fever persists and its origin is still obscure at the end of that period in a patient with a cardiac murmur a blood culture agglutination tests and other laboratory or roentgenologic studies should be made to confirm the tentative diagnosis of subacute bacterial endocarditis or to discover some other cause of the fever But unless or until some other cause is definitely demonstrated treatment should be undertaken for bacterial endocarditis Experience has taught that regardless of theoretical possibilities the diagnosis of bacterial endocarditis based on the above criteria is virtually always correct However the fever should be unequivocal (101 or higher) I have repeatedly seen these criteria misused in that the patient either had no organic murmur had unexplained fever for only a few days or had borderline fever (temperature up to 100°) Yet the diagnosis of bacterial endocarditis was supposedly based on these criteria The word ' unexplained in the above criteria is often neglected A patient with rheumatic valvular disease and fever who has a follicular tonsillitis does not have unexplained fever and bacterial endocarditis need not be invoked to explain it Bacterial endocarditis may occasionally be encountered in the absence of fever and in the absence of a cardiac murmur But in such cases the diagnosis cannot be made on the above criteria a positive blood culture must be obtained or other characteristic features of the disease must be present to justify the diagnosis

It should be stressed that if the diagnosis of bacterial endocarditis is considered most probable on the basis of the above criteria of a cardiac murmur and unexplained fever for more than a week, *80 to 90 per cent of possible* error or delay in diagnosis will be avoided provided only that blood cultures are taken For this is the percentage of cases in which the probable diagnosis will be confirmed by positive blood cultures The commonest cause of delay in diagnosis and treatment is failure to take blood cultures early enough because *the diagnosis of bacterial endocarditis is not* seriously considered If blood cultures are taken on two or three successive days when the temperature is highest and are negative, treatment for bacterial endocarditis should be undertaken while other diagnostic investigations are continued In the experience of Griffith and Levinson,[70] less than 3 per cent of the positive blood cultures were obtained after negative ones on the first two days

There is little risk that prolonged treatment will be undertaken unnecessarily If the diagnosis is in error, e g if the fever is due to rheumatic fever, there will be no response to the antibiotics and they can be discontinued If there is a prompt clinical response and one regards it as coincidence the antibiotic may be discontinued after four days If the fever recurs it is highly probable that the diagnosis of bacterial endocarditis was correct and that the clinical response was due to the antibiotic

Unexplained Fever in Heart Failure and in Rheumatic Children

There are two circumstances which may alter diagnostic probabilities If heart failure is definitely present long *before* the onset of the unexplained fever then other causes are more probable than bacterial endocarditis e g, pulmonary embolism or patchy bronchopneumonia In these circumstances of established heart failure the diagnosis of bacterial endocarditis must be based on positive blood cultures

A second modifying circumstance in the use of the criteria . unexplained fever for more than a week in association with an organic valvular murmur ' is the occurrence of these signs in children or teenagers who have experienced *a clinical attack of rheumatic fever* within five years In these patients recurrent rheumatic fever is at least as probable as bacterial endocarditis As a rule, however, in rheumatic fever there will be other distinctive features besides fever If not blood cultures will usually be positive if the fever is due to bacterial endocarditis If there are no distinctive *manifestations of rheumatic fever and blood* cultures are negative a therapeutic trial with

antibiotics may be made, the fever will not be controlled if it is due to rheumatic fever But the diagnosis of rheumatic fever will almost always prove erroneous in cases of prolonged unexplained fever in the adult

Diagnosis in the Absence of Murmur

In the absence of a cardiac murmur, the diagnosis may be extremely difficult The diagnosis depends on taking of blood cultures in all cases of unexplained fever and on the search for white-centered petechiae Osler nodes, hematuria splenomegaly, clubbed fingers or embolic phenomena The development of an organic cardiac murmur, not present previously is often the clue to diagnosis, but unfortunately a late one In doubtful cases of prolonged unexplained fever without a cardiac murmur it may be preferable to give the patient a therapeutic trial with penicillin as if he had bacterial endocarditis than to await serious and irreversible evidences of the disease

Blood Cultures

Blood cultures are important both for diagnosis and for determination of the causative organism and its sensitivity to specific antibiotics as a basis for effective treatment With proper technique positive blood cultures are obtained in 80 to 90 per cent of the cases of bacterial endocarditis The importance of the above-mentioned minimal diagnostic criteria would become readily apparent if they served only the purpose of initiating blood cultures after a week to ten days of unexplained fever in the patient with a cardiac murmur For then at least the 80 to 90 per cent of cases with positive blood cultures will be diagnosed and treated early Too often the delay in diagnosis is due to delay in taking blood cultures because the ' characteristic (late) symptoms have not yet appeared For management of the cases with negative blood culture, see page 884

Successful blood cultures require the use of aseptic techniques adequate amounts of blood (preferably 20 to 25 cc), a variety of fluid and solid media, some of which are enriched with dextrose, tomato liver, hormones ascitic fluid etc , anaerobic as well as aerobic conditions of growth prompt incubation and prolonged observation As a rule a positive culture will reveal growth within one to four days, but occasionally I have observed growth only after two or three weeks

Negative blood cultures in definite cases of subacute bacterial endocarditis[107] may be due either to improper technique or to absence or paucity of microorganisms in the blood at the moment of collecting the sample A positive blood culture requires the escape of a large number of bacteria into the blood from the focus on the valvular or mural endocardium Sometimes a positive culture of Streptococcus viridans may be obtained in the absence of bacterial endocarditis e g , in about 6 per cent of cases of rheumatic fever and other unrelated diseases according to Lichtman and Gross[1,4] Such transient bacterial invasions of the blood stream in normal individuals have also been noted following the extraction of teeth or tonsils Usually, however, in such cases the streptococci grow only in fluid media whereas in bacterial endocarditis they also appear in numerous colonies on the solid media

Differential Diagnosis

Subacute bacterial endocarditis must be distinguished from a host of diseases responsible for more or less prolonged fever and from numerous systemic diseases which are simulated by embolization of various organs

The most common errors are the diagnoses of "grippe," "virus infection' or influenza early in the course of the fever and active rheumatic fever when the fever persists In the *adult* with rheumatic heart disease bacterial endocarditis not rheumatic fever is almost always responsible for such fever A search for white-centered petechiae Osler nodes splenomegaly and microscopic hematuria, and cultures of the blood will usually distinguish subacute bacterial endocarditis Acute disseminated lupus erythematosus may resemble subacute bacterial endocarditis in the presence of prolonged fever, albuminuria and hematuria The finding of L E cells in the blood or marrow is diagnostic[79]

When the clinical picture is dominated by embolic involvement of a given organ, the following diagnostic errors are common (1) the diagnosis of a cerebral thrombosis or hemorrhage or meningitis when the onset or dominant symptoms are due to cerebral emboli m or rupture of a cerebral mycotic aneurysm (2) the diagnosis of chronic pyelonephritis chronic renal tuberculosis, glomerulonephritis or renal calculus disease with urinary infection when the onset or dominant manifestations of subacute bacterial endocarditis are due to renal vascular emboli or glomerular vascular lesions[109] In all such cases the finding of a cardiac murmur should put the examiner on

guard as to the possibility of a bacterial endocarditis Blood cultures and the search for other clinical manifestations will usually confirm this tentative diagnosis

Congestive heart failure may dominate the clinical picture and the causative bacterial endocarditis may be overlooked A careful history may disclose that continued fever preceded the heart failure and careful examination may disclose white centered petechiae splenomegaly etc Blood cultures must be taken in all cases of heart failure with continued fever

Difficulties in diagnosis arise because multiple diseases in elderly people mask the endocarditis In particular (1) occult neoplasm is diagnosed because of anorexia, weight loss anemia and fever, (2) congestive failure is diagnosed and attributed to coronary atherosclerosis or rheumatic cardiovalvular disease and (3) a cerebrovascular accident is diagnosed and attributed to cerebral atherosclerosis and infarction Despite these difficulties, the diagnosis will not be overlooked if the possibility of bacterial endocarditis is considered whenever there is a cardiac murmur and fever and if thereupon blood cultures are made as well as careful repeated observation for white centered petechiae Osler nodes and splenomegaly

The Bacteria Free Stage

Prior to the antibiotic era Libman[120] described a number of cases in the ' bacteria free stage presumably due to spontaneous healing The essential findings were a cardiac murmur, unexplained severe anemia brown pigmentation of the face splenomegaly and/or renal insufficiency Post-mortem examination revealed healed bacterial vegetations without bacteria similar to those vegetations now found sterilized and healed with the aid of antibiotics [124]

Recovered cases due to early adequate penicillin therapy should be distinguished from the spontaneous bacteria free stage because there need be neither heart failure renal insufficiency anemia nor splenomegaly Only the original valvular defect and subsequent bacterial damage remain However when treatment is delayed or the bacterial damage to valves myocardium or kidneys is too extensive by the time sterilization is accomplished with antibiotics persistent cardiac failure or renal insufficiency may develop as in the spontaneously bacteria free cases

TREATMENT

PRINCIPLES OF ANTIBIOTIC TREATMENT

The following principles should guide the use of antibiotics in treating subacute bacterial endocarditis

(1) Treatment should begin as early as possible before fatal or irremediable complications occur

(2) Adequate dosage should be administered i e , amounts which are suitable in each case to destroy the responsible organism found by blood culture The effective dosage is determined and modified by sensitivity tests repeated blood cultures and observation of the clinical course

(3) Antibiotic treatment should be continued long enough to sterilize completely all bacterial vegetations and all possible embolic foci

The rarity of spontaneous cure in bacterial endocarditis strongly indicates that the host s defense mechanisms are incapable of overcoming the infection by themselves This is probably due in large measure to the characteristics of the bacterial vegetation, in which bacteria are deeply enclosed in thick layers of fibrin which limit access of leukocytes and antibodies from the blood stream The relative avascularity of the subjacent valve tissue also prevents significant reaction of the host Because of the impotence of host factors cure depends almost exclusively on the exhibition of antibiotics in sufficient dosage to kill all the microorganisms before resistant strains appear Mere inhibition of growth of the organisms (bacteriostasis) is ineffective as they resume growth and multiplication as soon as the antibiotics are discontinued ■

Because of the nature of bacterial vegetation larger doses of antibiotic appear necessary to kill the microorganisms in vivo than in vitro Furthermore, antibiotics alone or in combination which sterilize microorganisms in broth cultures are ineffective when applied to the same organisms contained in infected clots [80] Chemical effects of the fibrin or mechanical impediment to diffusion of the antibiotic may account for the difference For these reasons also larger doses of an antibiotic are more effective than small doses in killing bacteria in clots even when both are equally effective in fluid media ■

Experimental studies of Eagle and associ

ates[47, 48] indicate that elimination of microorganisms from an infected focus depends on a sufficiently high concentration and on an adequate time of contact of this effective concentration of antibiotic with the organisms. They calculated that concentrations of 5 to 20 times that which inhibits growth of microorganisms in vitro are required to destroy these bacteria in vivo. Their studies and the studies of Weinstein et al.[203] on implanted fibrin clots in rabbits indicated, however, that effective concentrations of antibiotics need not be continuously present in order to eliminate the infection.

COMMENCEMENT OF TREATMENT

Early treatment demands early diagnosis (p. 876). When unexplained fever in a patient with a cardiac murmur has persisted for more than a week, blood cultures are made on two successive days, and therapy is begun immediately after blood is drawn for the second culture. If two properly performed blood cultures are negative, further blood or marrow cultures will rarely be positive. While the results of the blood cultures are awaited and treatment is initiated, other indicated diagnostic studies are carried out.

Treatment is begun with 2,400,000 units of aqueous procaine penicillin daily and 1 gm. each of streptomycin and dihydrostreptomycin in combination, all intramuscularly. If the blood culture is positive, the sensitivity of the organism to penicillin is determined. The choice of antibiotics and their dosage may be altered if necessary, according to these findings. If the blood cultures are negative, the clinical diagnosis should be reviewed. If bacterial endocarditis still appears probable, the dosage is continued if there is a favorable therapeutic response or increased if the response is unsatisfactory. Blood cultures should be repeated at weekly intervals or when there is a sharp rise in temperature.

SENSITIVITY OF THE CAUSATIVE ORGANISM

The sensitivity of the causative organism is determined in vitro by serial dilution in test tubes.[194] After incubating 1 cc. of the bacterial suspension with successive dilutions of antibiotic in different test tubes, one notes the lowest concentration of the antibiotic which inhibits growth of the organism as indicated by the absence of turbidity. That concentration is termed the sensitivity of the organism to the given antibiotic.

The sensitivity determined by this method is a measure of the concentration of antibiotic which is bacteriostatic for the given organism. However, to effect a cure in bacterial endocarditis it is necessary to attain levels which are bactericidal, i.e., actually kill the microorganisms, not merely inhibit their growth. In practice, one commonly attempts to attain plasma concentrations of antibiotic which are at least five, and preferably ten times as high as the bacteriostatic level determined by the sensitivity test. Usually such levels are bactericidal.

But when this empiric measure is ineffective, bactericidal levels should be determined directly. This is accomplished by mixing 1 cc. of the bacterial suspension with successive dilutions of the antibiotic. After a period to permit growth, the cultures on which there is no growth are subcultured into fresh media. Growth now occurs in those tubes in which the concentration was merely bacteriostatic. No growth occurs in those tubes in which the penicillin concentration was bactericidal. As a rule, particularly with respect to penicillin and the non-hemolytic streptococcus, these bactericidal levels in vitro correspond fairly well to the concentrations which are effective in vivo. But clinical effectiveness is the final determinant of adequacy of antibiotic dosage, not the in vitro bacteriostatic or bactericidal sensitivity.

DETERMINATION OF SERUM LEVEL OF PENICILLIN AND BACTERICIDAL EFFECT OF SERUM

The penicillin level in the blood can be determined after therapy is begun. Of a series of tubes containing 0.8, 0.7, 0.6 cc. of serum, etc., each is made up to 1 cc. with broth and mixed with a 1 cc. suspension of a young culture of the test organism. The 2 cc. mixtures are incubated for 24 hours and the lowest concentration of serum required to inhibit the growth of the standard organism is observed. Since the sensitivity of the standard organism is known in terms of Oxford units, it is possible to calculate the number of Oxford units of penicillin per cubic centimeter of serum. Or else the same procedure is repeated using known concentrations of penicillin in broth in place of the body fluid. If the amount of serum

and the known concentration of penicillin necessary to inhibit the same bacterium in the same test volume are equated, the concentration of penicillin in serum can be calculated Experience and knowledge of the dose of penicillin administered facilitate the arrangement, in advance of the proper range of serum dilutions to be used in the test

In some cases it is desirable to determine whether the concentration of penicillin in the plasma is actually capable of killing the causative microorganism The test is made as above to determine the bactericidal effect of various concentrations of antibiotic But instead of adding antibiotic, serum in various dilutions is used to determine its bactericidal effect on cultures of the causative organism It is desirable that the serum be bactericidal even when diluted 1 4

ANTIBIOTIC TREATMENT ACCORDING TO CAUSATIVE ORGANISM

Sensitive Non hemolytic Streptococci

Penicillin remains the drug of choice in the treatment of sensitive non hemolytic streptococci i e usually the Streptococcus viridans salivarius or mitis Sensitive non hemolytic streptococci may be arbitrarily regarded as those which are sensitive to 0 1 unit of penicillin per cubic centimeter or less Although a successful outcome of bacterial endocarditis due to a sensitive streptococcus would usually follow treatment with 1 million or 500 000 units a day experience has taught that a maximal percentage of successful results would be obtained if the dosage is about 1 or 2 5 million units a day [1] Formerly I administered 4 cc (1 200 000 units) of aqueous procaine penicillin intramuscularly every 12 hours for five or six weeks Or rarely 2 5 million units of aqueous potassium or sodium penicillin was dissolved in 1000 cc of 5 per cent glucose in water and administered continuously each 24 hour period for five or six weeks

In the past few years I have successfully treated bacterial endocarditis due to sensitive non hemolytic streptococci over a two week period only The earliest reports of effective therapy of bacterial endocarditis with penicillin indicated that an average dose of only 200 000 units of penicillin a day for only two weeks effected a cure in about 75 per cent of cases [126] But both dosage and duration of treatment were progressively increased in order to obtain maximal effectiveness More recently Hamburger and Stein[76] cured 10 of 12 patients with bacterial endocarditis due to sensitive microorganisms in 11 to 14 days by the administration of 15 to 16 million units of crystalline penicillin daily Geraci and Martin[64] cured 18 of 23 patients of bacterial endocarditis due to penicillin sensitive streptococci with 1 2 to 2 4 million units of penicillin and 1 2 to 2 4 gm of dihydrostreptomycin daily in divided doses This was supplemented by a report[6] of 23 additional consecutive patients with bacterial endocarditis caused by penicillin sensitive streptococci who were treated for two weeks with 1 million units of aqueous procaine penicillin and 1 gm of combined streptomycin-dihydrostreptomycin (0 5 gm each) administered intramuscularly every 12 hours Twenty patients recovered

I have been regularly treating all patients with bacterial endocarditis due to streptococci with sensitivities of 0 1 unit or less by administering 1,200 000 units of aqueous procaine penicillin and 0 5 gm each of streptomycin and dihydrostreptomycin (i e 1 gm of Distrycin or Combistrep) intramuscularly every 12 hours for two weeks In all cases of bacterial endocarditis the recommended antibiotic and dosage are continued only if there is clinical evidence of effectiveness Increased resistance of Streptococcus viridans (alpha) is rarely observed in the course of treatment [44] Neither has there been a significant change in penicillin susceptibility of these microorganisms in the past ten years [8]

The oral administration of penicillin has not hitherto been regarded as a satisfactory method of treating bacterial endocarditis because of incomplete or unpredictable absorption from the gastrointestinal tract The recently developed phenoxymethyl penicillin (penicillin V) was found to yield substantially higher and more prolonged blood levels of penicillin when given orally than penicillin G In two patients with endocarditis due to penicillin sensitive alpha hemolytic streptococci 12 million units of penicillin V orally each day (2 million units i e 4 tablets every 4 hours) for six weeks effected a cure [157] A third patient with endocarditis due to a more resistant organism was cured by a combination of penicillin V orally and streptomycin intramuscularly In a fourth case due to a penicillin resistant micrococcus penicillin V was ineffective

Clinical Response to Penicillin. In favorable

cases the patient's general condition improves and his appetite and sense of well being are restored within a day or two after treatment is begun Blood cultures may become sterile within 4 hours and usually within 24 hours Fever usually subsides by the end of a week, it may persist as long as penicillin is being administered, but at lower levels than before treatment In the absence of continued active bacterial endocarditis or of bacterial emboliza tion persistent fever may also be due to throm bophlebitis at the sites of venoclysis, inflammation at the sites of intramuscular injections, or concomitant intercurrent upper respiratory or other infection Petechiae and emboli usu ally cease after the first week of successful therapy but may recur for many weeks even in cases with favorable outcome Despite these exceptions persistent fever, embolization and petechiae should stimulate a review of the adequacy of penicillin dosage With a favor able response to penicillin, the hemoglobin rises, leukocytosis subsides and the sedimenta tion rate falls But the latter may not return to normal for several weeks after treatment is discontinued

The question of penicillin sensitivity has rarely been a problem Urticarial and other skin lesions may be controlled by the simul taneous administration of antihistamines orally or by injection [7] More severe lesions may require the simultaneous use of steroid hormones (prednisone, etc) Hypoallergenic peni illin O may be tried, but there is often cross sensitization It must be especially emphasized that bacterial endocarditis is a fatal dis ease and usually there is no substitute for penicillin to effect a cure Therefore, no his tory of penicillin sensitivity should be accepted as an adequate reason for withholding penicillin therapy unless one is certain that some other antibiotic is equally effective Rarely, gradual desensitization against penicillin may have to be undertaken but I have never found this necessary in an extensive experience with the treatment of bacterial endocarditis

Relatively Resistant Non hemolytic Streptococci—Enterococci (Streptococcus Fecalis)

When the causative streptococcus is sensitive to concentrations above 0 1 unit per cubic centimeter it may be classified as relatively resistant Most enterococci are sensitive to 1 to [illegible] units of penicillin per cubic centimeter, i e, they are 50 to 250 times as resistant to penicillin as the standard organism Even larger concentrations are required for a bac tericidal effect and many strains of enterococci are not completely destroyed by any reason able concentration of penicillin alone On the other hand, although streptomycin itself has no bacteriostatic effect on resistant entero cocci it has a potentiating effect on penicillin and the combination is bactericidal in vitro[illegible] and in vivo[illegible, 162, 127]

Bacterial endocarditis due to the enterococcus or other relatively resistant non hemolytic streptococcus is usually cured by the administration of 6 to 10 million units of penicillin daily, and 2 gm of streptomycin-dihydrostreptomycin mixture daily, for a period of six weeks As a rule, when the sensitivity is more than 2 units of penicillin per cubic centimeter, I administer 15 to 25 million units of penicillin daily with the 2 gm of streptomycin dihydrostreptomycin Occasionally, when the organism is inhibited by 5 units of penicillin per cc or more, or is not completely inhibited even by 10 units of penicillin per cc, it may be necessary to use massive doses of 50 to 100 million units of penicillin daily with the streptomycin Aside from these sensitivity studies the clinical response often determines the need for massive doses of penicillin In one patient with bacterial endocarditis due to a very resistant Streptococcus viridans, 25 million units of penicillin daily with 2 gm of streptomycin dihydrostreptomycin and 2 gm of Benemid orally for six weeks eliminated fever and resulted in negative blood cultures throughout the period of treatment However, there was a relapse in 19 days with recurrence of fever and positive blood cultures Cure was effected by a daily penicillin dosage of 50 to [illegible] million in combination with streptomycin and bacitracin

Ordinarily the larger doses of penicillin are best administered by dissolving the daily dose of aqueous potassium penicillin (available in 5 million unit vials) in 1000 cc of 5 per cent dextrose in water and administering by slow intravenous drip The total daily fluid intake is modified as indicated Streptomycin 0 5 gm and dihydrostreptomycin [illegible] 5 gm (1 gm of Distrycin or Combistrep) are administered intramuscularly every 12 hours during the period of penicillin therapy Except with very resistant organisms the streptomycin is dis continued after four weeks but the penicillin

is continued for six weeks With moderately resistant organisms the streptomycin-dihydrostreptomycin mixture may be reduced from 2 gm daily to 1 gm daily after two weeks

Occasionally with the enterococci of lesser resistance in which 6 million units of penicillin are given daily, the drug may be administered intramuscularly as concentrated penicillin (e g Abbocillin 800 000 units per cc) 2 cc (1,600 000 units) being given every 6 hours The streptomycin-dihydrostreptomycin is given simultaneously as above

When the penicillin streptomycin combination is ineffective or streptomycin or dihydrostreptomycin must be discontinued because of vestibular or auditory disturbances, respectively cure of enterococcus endocarditis can usually be accomplished by use of the abovementioned doses of *penicillin in combination with 60 000 units daily of bacitracin intramuscularly* [190] Renal function and urinary output must be followed carefully because of the nephrotoxicity of bacitracin

In rare instances other antibiotic combinations have been used and found effective in curing enterococcal endocarditis after penicillin combinations had failed In one case cure was effected by a combination of erythromycin (1 gm intravenously twice daily) chlortetracycline (0 5 gm every 6 hours) and streptomycin (0 5 gm intramuscularly twice daily) [188] Ahern and Kirby[1] reported cure of bacterial endocarditis due to a resistant Streptococcus viridans with 1 800 000 units of penicillin intramuscularly and 1 gm of chloramphenicol orally every six hours Erythromycin administered intravenously (4 gm daily) may be effective (p 886)

Probenecid (Benemid) Drugs which diminish the renal excretion of penicillin have been employed as adjuvant therapeutic agents to *obtain increased concentrations of penicillin in* the blood This is rarely necessary now because of the ready availability and ease of administering large doses of penicillin Benemid has been found capable of enhancing the penicillin blood level between two and three times when administered orally in doses of 0 5 gm [195, 12] every 6 hours for a total of 2 gm daily It does not increase the blood level of streptomycin or of the broad spectrum antibiotics Occasionally it produces nausea epigastric burning and other symptoms of indigestion

Staphylococcal Endocarditis

Penicillin alone, in a daily dose of 2 4 million units (1 200 000 units of aqueous procaine penicillin intramuscularly every 12 hours) for six weeks is effective in curing endocarditis due to sensitive staphylococci For the increasing number of cases due to highly resistant staphylococci (micrococci), i e resistant to penicillin, treatment is guided by studying the in vitro sensitivity to various antibiotics alone or in combination As a rule I begin by administering massive doses of penicillin (50 to 100 million units daily) together with erythromycin in doses of 3 to 4 gm daily and continue this if fever is controlled and blood cultures become negative The erythromycin may be given intravenously (p 886) If this antibiotic is ineffective I switch to chloramphenicol (Chloromycetin), chlortetracycline (Aureomycin), oxytetracycline (Terramycin) or tetracycline (Achromycin) according to the sensitivity studies Miller and associates[186] reported 3 cured cases of staphylococcal endocarditis 2 of them cured by means of chloramphenicol Not infrequently the simultaneous administration of two or more antibiotics is effective when none of these alone is curative Erythromycin and chloramphenicol given orally, or with bacitracin administered intramuscularly at the same time as this combination is given orally have been effective The addition of bacitracin cured a fulminating case of acute staphylococcal endocarditis after huge doses of penicillin and Aureomycin were ineffective by themselves [16] Johnson and Hurst[93] reported a cure of staphylococcus endocarditis treated with streptomycin, erythromycin and oxytetracycline the latter two given intravenously If these are ineffective, I administer 15 to 25 *million units* or more of penicillin daily in combination with 60 000 units of bacitracin daily intramuscularly Rarely penicillin and neomycin or neomycin alone may be effective when other antibiotics have failed [190] In acute cases of bacterial endocarditis the course may be so fulminating that there is no time to experiment and multiple antibiotics are used with successive addition of new antibiotics when a clinical response is not obtained Treatment is continued for six weeks after blood cultures become negative and the clinical manifestations are controlled

The treatment of endocarditis due to the rarer bacterial causes is noted in Table 8

Table 8 Antibiotics According to Causative Microorganism[15]

ANTIBIOTIC	DAILY DOSE	DURATION WEEKS
Sensitive Non hemolytic Streptococci (0 1 u /cc or less)		
Penicillin	2 400 000	4 to 6
Penicillin plus Streptomycin	2 400 000 plus 2 gm	2
Streptococcus fecalis and Other Resistant Non hemolytic Streptococci		
Penicillin plus Streptomycin plus Dihydrostreptomycin	6–75 million; 1 gm; 1 gm	4 to 6
Penicillin plus Bacitracin	6 to 75 million; 60 000	4 to 6
Staphylococcus (Penicillin-Sensitive)		
Penicillin	2 400 000	4 to 6
Staphylococcus (Penicillin Resistant)		
Aureomycin	3 to 4 gm	6
Chloramphenicol	3 to 4 gm	6
Penicillin plus Bacitracin	2 to 10 million; 60 000	4 to 6
Erythromycin	3 to 4 gm	4 to 6
Streptococcus hemolyticus		
Penicillin	2 400 000	4 to 6
Penicillin plus Streptomycin	6 000 000; 2 gm	4 to 6
Pneumococcus		
As for Streptococcus hemolyticus		
Meningococcus		
Penicillin plus Sulfonamides	2 400 000; 2 to 4 gm	4 to 6
Hemophilus influenzae parainfluenzae Klebsiella (Friedländer) Brucella		
Streptomycin plus Broad spectrum antibiotics	2 gm; 3 to 4 gm	2 to 6
Streptobacillus moniliformis Pasteurella		
Aureomycin or Terramycin or Achromycin	3 to 4 gm	4 to 6
Salmonella Pseudomonas Escherichia Aerobacter Proteus		
Chloramphenicol plus Streptomycin plus Neomycin	3 to 4 gm; 2 gm; 1 to 2 gm	4 to 6
Pseudomonas aeruginosa		
Polymyxin	2 to 5 mg /kg	4 to 6

TREATMENT OF ENDOCARDITIS IN CASES WITH NEGATIVE BLOOD CULTURES

Treatment is usually begun with 2 4 million units of penicillin and 2 gm of streptomycin combination daily, while the results of blood cultures are awaited If these are persistently negative, *one of three courses may be taken*

1 If the clinical response is satisfactory the treatment is continued *for two weeks* in the hope that we are dealing with a sensitive streptococcus If there is a relapse after the two weeks' course, retreatment is undertaken with larger doses of penicillin for a period of six weeks

2 If the clinical course is unsatisfactory and fever persists unabated 6 to 25 million units of penicillin daily are given in increasing doses in combination with the streptomycin until the fever is controlled If these increased doses are ineffective, various antibiotics are tried as if the causative organism were a resistant staphylococcus As a rule, there is a good clinical response with moderate doses of penicillin and streptomycin confirming the presence of bacterial endocarditis or else no response with any antibiotic indicating the need for a continuing search for some other cause of the fever

3 If there is a prompt clinical response and disappearance of fever and the skeptic thinks that this is coincidental he may discontinue the antibiotics after four days The temperature should remain normal if its fall was spontaneous, but will soon rise again if there is bacterial endocarditis and will be controlled again by the previously effective antibiotic In the latter circumstance treatment is resumed and completed as in cases of proven bacterial endocarditis

In the absence of positive blood cultures and a favorable response to penicillin and streptomycin other antibiotics are tried at random, but sometimes the clinical history may suggest the possible causative organism and indicate a choice of antibiotic Some of the factors in the history suggesting the causative organism are noted in Table 9

Table 9 Factors in History Suggesting Causative Organism[16]

Dental Extraction	*Boils Nail-biting*
Streptococcus viridans	Staphylococci
Streptococcus fecalis	*Epidermophytosis*
Intestinal Procedures	Staphylococci
Streptococcus fecalis	Streptococcus hemolyticus
Escherichia coli	
Urologic Procedures	*Narcotic Addicts*
Streptococcus fecalis	Staphylococci
Abortion	Yeasts
Streptococcus fecalis	*Exposure to Rats*
Staphylococcus aureus	Spirillum
Corynebacteria	Streptobacillus moniliformis
Anaerobic streptococci	
Cat Bite	
Pasteurella	

INDIVIDUAL ANTIBIOTICS

Penicillin

This is the drug of choice for the treatment of bacterial endocarditis due to streptococci (Str hemolyticus, Str viridans and enterococci), sensitive micrococci (staphylococci) pneumococci and gonococci

Streptomycin and Dihydrostreptomycin are rarely used alone but may be effective in doses of 2 gm daily for two to four weeks in cases due to Hemophilus influenzae[113] and parainfluenzae and Klebsiella (Friedlander's bacillus) They are widely used in combination with penicillin in cases due to non hemolytic streptococci especially enterococci Brucella endocarditis may be treated by streptomycin dihydrostreptomycin in combination with chlortetracycline[84] Resistance to streptomycin is less likely to develop when this antibiotic is used in combinations than when it is used alone The physician should be alert to the risk of damage to the vestibular nerve by streptomycin or to the auditory nerve by dihydrostreptomycin These complications have been extremely rare in my experience when the drugs were used in doses not exceeding 2 gm daily for four weeks There is evidence that the toxicity from both agents may be reduced without diminished effectiveness if the total dose is divided equally between the two preparations e g 0 5 gm of each every 12 hours

Broad Spectrum Antibiotics chlortetracycline[104, 84, 8] oxytetracycline[61] tetracycline[115] and chloramphenicol[104, 130] are bacteriostatic and not bactericidal in cases due to the Streptococcus viridans or enterococci Despite a good clinical response and negative blood cultures while these antibiotics are being administered, as a rule there is a relapse within a week after discontinuing therapy Regardless of reported sensitivity or temporary clinical response they should not be used as the primary drug in such cases even though they are occasionally effective[156, 84] They may be tried if large doses of penicillin with streptomycin have been ineffective The usual dose is 2 to 4 gm daily orally or 1 gm daily intravenously They may be effective against staphylococci (micrococci) and may be used as the primary drugs in occasional cases due to Streptobacillus moniliformis (Actinomyces muris) caused by a rat bite or Pasteurella endocarditis due to a cat bite Because chloramphenicol fell into disuse on account of reported bone marrow depression fewer strains of staphylococci appear to have developed resistance to this than to other broad spectrum antibiotics Chloramphenicol and other broad spectrum antibiotics are also employed in doses of 4 gm

daily in combination with streptomycin 2 gm daily in cases of bacterial endocarditis due to Brucella organisms Acute bacterial endocarditis due to C diphtheriae has been treated successfully by chloramphenicol in combination with penicillin and streptomycin[35]

Bacitracin (15 000 units intramuscularly every 6 hours) may be employed in combination with very large doses of penicillin in the treatment of endocarditis due to resistant staphylococci [illegible] or to enterococci resistant to penicillin and streptomycin A patient with diphtheroid endocarditis was cured by bacitracin after failing to respond to a combination of penicillin and streptomycin[210] Occasionally bacitracin causes anorexia, nausea or vomiting, and in one patient I treated with large doses of penicillin and bacitracin it may have been responsible for a hemolytic anemia The common risk is renal damage and the urinary output and blood urea nitrogen should be followed carefully Albuminuria is not a contraindication to its continued administration

Erythromycin (Erythrocin, Ilotycin) is antimicrobial chiefly against gram positive microorganisms, its range of effectiveness resembling that of penicillin It may be effective orally (2 to 4 gm daily for six weeks) in the treatment of staphylococcus endocarditis resistant to penicillin, particularly when used in combination with chloramphenicol streptomycin or bacitracin *Erythromycin lactobionate* may be given intravenously in doses of 300 to 500 mg every 6 to 8 hours But the action of erythromycin alone is predominantly bacteriostatic, not bactericidal[100] Furthermore, increase in the resistance of staphylococci has been noted[74] *Erythromycin glucoheptonate* may be administered intravenously Bishop et al[9] reported recovery in a case of subacute bacterial endocarditis due to an extremely resistant non hemolytic streptococcus as a result of therapy with this erythromycin, given by a continuous intravenous drip in a daily dosage of 4 gm for six weeks after numerous antibiotics had failed

Neomycin sulfate administered in doses of 250 to 500 mg intramuscularly every [illegible] hours may be considered in the treatment of endocarditis caused by Salmonella, Pseudomonas, Escherichia, Aerobacter, Klebsiella and Proteus vulgaris In combination with large doses of penicillin it may be effective against otherwise resistant staphylococci Reed and Wellman[180] reported cure of a patient with endocarditis caused by a staphylococcus resistant to all other common antibiotics, by the administration of 250 mg neomycin intramuscularly every 6 hours for one week and 125 mg every 4 hours for an additional four weeks Some hearing impairment developed Neomycin is a toxic drug, to be used only in otherwise fatal cases which do not respond to safer antibiotics It may produce deafness or renal insufficiency[102] The total daily dosage of 2 gm is given in divided doses intramuscularly at 6 hour intervals

Polymyxin is another toxic antibiotic which may be considered if one encounters a case of bacterial endocarditis due to gram negative bacilli, especially Pseudomonas aeruginosa (B pyocyaneus) One may give 2 to 5 mg per kilogram intramuscularly daily in four to six divided doses, but no individual dose should exceed 1 mg kg body weight Careful observation should be made for possible renal toxicity The drug must be discontinued if there is [illegible] sharp reduction in urinary output or a rise in the blood urea nitrogen

Sulfonamides may be employed in combination with broad spectrum antibiotics and penicillin in cases of meningococcic endocarditis

SURGICAL TREATMENT

Ligation and section of a patent ductus arteriosus has cured patients with subacute bacterial endarteritis associated with this congenital defect[188] Surgical ligation cures not only the infection in the ductus and pulmonary artery but also the anatomic and the resulting physiologic and clinical disturbances If the causative organism is sensitive treatment should begin with antibiotics and surgical ligation should be performed at a later date to eliminate existing symptoms and to avoid subsequent reinfection or circulatory disturbances

Resection of an infected arteriovenous aneurysm has cured cases of subacute bacterial endarteritis engrafted on the aneurysm[77, 187, 181] Delayed treatment may mean secondary infection of the heart valves with bacterial endocarditis as well as endarteritis As with an infected patent ductus, antibiotic therapy should be instituted if the organism *is* sensitive Later, excision of the aneurysm is indicated to avoid reinfection and circulatory insufficiency

Mycotic emboli and aneurysm occasionally require surgical removal or excision while the general infection is controlled by antibiotic therapy The successful excision of a mycotic aneurysm of the brachial artery following cure of a bacterial endocarditis was reported by Hurwitz and Arst [91]

Splenectomy was followed by cure in 3 patients with typical bacterial endocarditis in whom fever and positive blood cultures had persisted despite high blood levels of anti biotics because of infected splenic infarcts [1-5]

PROPHYLACTIC TREATMENT

Prophylactic treatment is indicated in all subjects with rheumatic cardiovalvular or with congenital heart disease, for they are the ones likely to contract bacterial endocarditis Manipulations and operative procedures, es pecially dental extractions tonsillectomy, cystoscopy, lithotomy or prostatectomy, cu *rettage or childbirth are likely to inject organ* isms into the blood stream which lodge on a valve or blood vessel and form bacterial vege tations Penicillin should be administered shortly before and for 48 hours after the pro cedure However the dosage and duration of treatment are empirical and the effectiveness of therapy is uncertain Fifty thousand units of penicillin intramuscularly every two hours in the 24 hours *preceding* dental extraction failed to prevent bacteremia although it diminished its incidence [85] I now recommend that 4 cc of Combiotic (600 000 units of pro caine penicillin, 200 000 units of aqueous peni cillin and [illegible] gm of streptomycin) be given in tramuscularly one half hour before the actual procedure since the invasion of the blood stream is transient and occurs within a few minutes after the manipulation Larger doses may be required to prevent growth of resistant organisms The same dose should be repeated 24 hours later Pressman and Bender[154] have recommended in addition that extraction trauma be minimized not more than one tooth being extracted at a time with minimum rocking and that local antibiotic be intro duced into the gingival sulcus by means of a troche of penicillin sulfadiazine and bacitra cin one-half hour before extraction The American Heart Association now recommends the administration of 600 000 units of aqueous penicillin and 600 000 units of procaine peni cillin in oil containing 2 per cent aluminum monostearate administered intramuscularly 30 minutes before the operative procedure As a less desirable alternative buffered penicillin may be administered orally 250 000 to 500 000 units one half hour before each meal and at bedtime beginning 24 hours prior to operation and continuing for five days At the time of operation an additional 250 000 units should be given Broad spectrum antibiotics should be used prophylactically in patients who are sensitive to penicillin or about to undergo surgery of the urinary or lower intestinal tract in full dosage for five days beginning the day before the surgical procedure

In patients who undergo genitourinary procedures, prophylactic antibiotics should be given with special awareness of the danger of enterococcal endocarditis in those with or without preexistent valvular disease One million units of penicillin and 1 gm of strepto mycin should be given one hour before the procedure and repeated every 12 hours until *24 hours after the manipulation and operation* are completed and the catheter removed

Patients who are already suffering from bacterial endocarditis should be carefully ex amined for foci of infection The necessary extraction of teeth or tonsils drainage of sinuses or urologic procedures should be per formed while the patient continues to receive effective antibiotic treatment

PROGNOSIS

The outlook has dramatically improved since penicillin became available Through 1945 *elimination of the infection* was achieved in 107 (81 7 per cent) of 131 cases reported by six different groups of observers At the pres ent time it is probable that the infection can be controlled in about 90 to 95 per cent if death does not occur before two weeks of treatment but recoveries are actually being effected in only about 65 to 75 per cent of cases [33, 42, 140, 11] In Wagner's[19] review of 469 cases of subacute bacterial endocarditis only 4 5 per cent were therapeutic failures due to the resistance of the organism Since blood levels of 35 units per cubic centimeter of peni cillin or more can be attained with huge doses of this drug and since other antibiotics are available it is probable that the number of resistant organisms causing bacterial endo carditis will become minimal

The *percentage of clinical recoveries* is smaller than the percentage of bacteriologic cures Wagner[192] collected 371 reported recoveries

(71 3 per cent) among 469 cases Christie[5] collected 81 recoveries (55 per cent) among the first 147 unselected cases treated in Great Britain Jones et al[93] found reports of 266 recoveries (65 5 per cent) among 406 cases In an analysis of 52 treated cases Newman et al[140] observed that although 69 per cent were cured of their bacterial infection, one third of those cured died of heart failure one third were alive but disabled by the residuals of the disease and only 23 per cent of the adequately treated cases were returned to an asymptomatic state

At first therapeutic failures were due chiefly to inadequate dosage and high resistance of the organism with consequent persistence of the infection At present the most important *cause of failure is delay in treatment* [illegible][5] Priest et al[156] found that the average duration of the disease before the beginning of treatment was 9 2 weeks in a group of recovered cases and 22 5 weeks in a group of fatal cases During the period of delay progressive valvular damage and toxic, vascular and inflammatory lesions of the heart muscle lead to irreversible heart failure, extensive vascular renal damage leads to uremia, or suppurative embolic lesions suppurative pericarditis or deep seated valvular or myocardial suppuration causes sudden death or uncontrollable infection[21, 3] Bunn and Cook[19] reported that rupture of the aortic valve caused death in 6 of 15 fatal cases Thus the outlook becomes more and more favorable the earlier the diagnosis is made and adequate treatment begun

Assuming that adequate blood levels of penicillin can be obtained to inhibit growth of the causative organism, there is no close relationship between the degree of sensitivity of the organism and the likelihood of recovery The presence of complications before treatment is begun such as heart failure frequent and serious embolizations, suppurative pericarditis or ruptured valves denotes a poor prognosis Recovery may occur despite previous failures with penicillin, provided that the causative organism is sensitive to practical doses of antibiotics and no incurable complications have developed Age and sex are usually insignificant for prognosis, but patients beyond the age of 50 are not as likely to recover as younger persons Recoveries occur about equally when the disease complicates rheumatic or congenital lesions

Relapses usually occur, if at all, in the first four weeks after discontinuing treatment Rarely relapses seem to develop as late as three months afterward Clinical and bacteriologic cure for six months after treatment almost always denotes permanent recovery from the given attack Christie[25] estimated that a slight risk, amounting to about 2 per cent per annum, of relapse or reinfection, remained

If recovery occurs without serious complications, the ultimate outlook is determined, not by the residuals of the bacterial infection, but by the nature and severity of the preexisting cardiac disease and subsequent disease[135, 140] The long term outlook is favorable if the patient recovers from the bacterial endocarditis with no heart failure, renal insufficiency, serious embolic complication or free aortic *regurgitation which was not previously present*

Cause of Death

In the fatal cases, death is most commonly due to congestive heart failure This may develop during or after treatment Other causes of death are renal insufficiency and uremia, embolization, especially rupture of mycotic aneurysms of the cerebral vessels with subarachnoid or cerebral hemorrhage, and persistent infection Sudden death is uncommon but may be due to coronary or cerebral embolism or rarely to heart block with ventricular standstill, or to rupture of a splenic infarct

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Chapter 35

SYPHILIS OF THE HEART AND AORTA

Education, public health measures and drugs have sharply reduced the incidence of syphilis As the incidence has diminished and as early syphilis has been effectively treated, cardiovascular syphilis has become scarce It probably accounts for less than one half of 1 per cent of heart disease in most parts of the United States except the south Even in the south the incidence of syphilitic cardiovascular disease has been sharply reduced

Syphilitic heart disease is rarely a primary disease of the heart resulting from gummatous or diffuse inflammatory lesions of the myocardium In the vast majority of cases clinical syphilitic heart disease is secondary to syphilitic infection of the aorta (luetic aortitis) and its complications

Syphilitic aortitis has been found at autopsy in more than 75 per cent of untreated cases of syphilis[illegible] Clinically, however, evidence of cardiovascular involvement is observed in only 10 per cent of patients with late syphilis[93, 8]

ETIOLOGY OF AORTIC SYPHILIS

Cause and Pathway of Infection

The organism responsible for cardiovascular syphilis is the Treponema pallidum (Spirochaeta pallida) The organisms enter the blood stream early in the disease, for excision of the chancre does not prevent the development of secondary and tertiary syphilitic lesions The treponemata localize frequently in the ascending aorta but only very rarely in the myocardium It is probable that the spirochetes reach the lungs where they are filtered out into the mediastinal lymph nodes From there they are borne by retrograde extension into the perivascular lymph spaces around the vasa vasorum of the ascending aorta[84] The lymphatic spread of the microorganisms explains their predilection for the aorta and the rarity of endocardial and myocardial lesions for the microorganisms do not attack the cardiovascular system from within the heart or great vessels

The Latent Period Between ten and twenty five years often elapse between the onset of the primary syphilitic infection and the appearance of clinical manifestations of cardiovascular disease This so-called latent period does not denote quiescence of the infection It is more probable that progressive inflammation, tissue destruction and scar formation occur from the onset, but that clinical symptoms and signs appear only when the aortic lesions are sufficiently severe and extensive or involve the coronary ostia and aortic valves

Occasionally the latent interval is relatively short[85] In a study of 142 individuals with syphilis of the aorta in whom the onset of the infection could be determined accurately there were 3 patients who developed clinical syphilitic aortitis within five years[17] In rare instances syphilitic aortic aneurysm or insufficiency occurred within a year or two after the primary infection[43] The appearance of clinical manifestations of cardiovascular syphilis should be regarded not as the beginning but as the advanced stage of a protracted progressive disease of the aorta

Age and Sex Syphilitic heart disease is most frequent between the ages of 35 and 55[107] However, acquired cardiovascular syphilis has been reported beyond the age of 70[113] and as early as 20 Cardiovascular syphilis affects males predominantly in the ratio of between 2 to 1 and 5 to 1 This has been attributed to the higher incidence of primary syphilis among men to the greater stress of their physical work, to greater indulgence in tobacco and alcohol and to constitutional differences

Other Etiologic Factors. There is a much higher incidence in this country among Negroes than among white individuals.[11] It is probable that this is due not to racial differ

ences but to the poorer economic and social status of the former Among both groups syphilitic heart disease is encountered with increasing frequency the lower the social level and the greater the hardship

Inadequacy of Early Antisyphilitic Therapy

Failure to treat early syphilis and inadequate treatment are prime factors in the occurrence of cardiovascular syphilis Studies of patients with cardio-aortic syphilis indicate that almost all of them had no antisyphilitic treatment at all or only sporadic inadequate therapy [16] Moreover comparative studies of the course of patients with and without completely satisfactory antiluetic therapy disclose a much lower incidence of cardiovascular syphilis in the properly treated group [5]

Association of Cardio-aortic Syphilis and Syphilis of the Central Nervous System

Straub's[97] emphasis on the frequent association of luetic aortitis with neurosyphilis was influential in demonstrating the syphilitic nature of the aortitis In a report by Cole and associates [18] there were 642 patients with cardiovascular syphilis of whom 43 per cent also had syphilis of the central nervous system Conversely studies of patients with neurosyphilis have disclosed that a significant per centage have evidence of syphilitic aortitis and its complications [9]

Cardio aortic Disease in Congenital Syphilis

Aortitis, myocarditis cardiac gummata and cardioaortic aneurysms have been *reported in* congenital syphilis [109] Most of these were clinically insignificant occurring in infants who died shortly after birth Congenital syphilis rarely produces cardio aortic lesions of the type seen in acquired syphilis In 4000 post-mortem examinations at the Johns Hopkins Hospital Norris[7] found only 2 instances of luetic aortitis which were presumably of congenital origin McCulloch[69] found that only 8 of 32 syphilitics dying before the age of 2 showed syphilitic cardiac lesions at autopsy None of his patients up to the age of 15 developed clinical evidences of cardiovascular syphilis Dominguez and associates[29] described clinical and postmortem observations on an 18 year old girl with distinct signs of aortic aneurysm and aortic insufficiency caused by congenital syphilis

PATHOLOGY OF CARDIO AORTIC SYPHILIS

The lesions of cardio aortic syphilis include those which originate in the aorta and those which arise directly in the myocardium The former consist of luetic aortitis and its complications namely insufficiency of the aortic valve stenosis or occlusion of the coronary orifices and aortic aneurysm The primary myocardial lesions are gummata and syphilitic myocarditis The endocardium and pericardium are rarely involved and then only by extension of the above myocardial and aortic lesions

SYPHILITIC AORTITIS

Gross Pathology

The naked eye appearance of syphilitic aortitis is generally sufficiently characteristic to permit a definite diagnosis on gross examination Often syphilitic aortitis is associated with atherosclerosis and calcification The distinctive features are (1) the bluish gray or porcelain gray intimal plaques, (2) the wrinkling and puckering of the inner aspect of the aorta with a tendency to form radial or parallel grooves the latter in the direction of the long axis of the aorta, (3) the sharp transverse demarcation of the aortic lesions ending at the origins of the vessels of the neck at the level of the diaphragm or at the origin of the renal arteries (4) the localization of the most extensive lesions to the ascending aorta above the sinuses of Valsalva, and the progressive diminution of le ions as one proceeds along the course of the transverse and descending *thoracic aorta*

The wall of the aorta is irregularly thickened by the plaques and thinned out where it is grooved and puckered It may be so thin that it becomes translucent When the lesions are extensive the aorta loses its elasticity and becomes widened and flaccid This widening is irregular and may be localized particularly to the ascending aorta, or it may be diffuse Rarely there is a gummatous type of aortitis [104]

Microscopic Pathology

1 **Adventitial Changes** The primary lesion probably occurs around the vasa vasorum of the adventitia There are perivascular infiltrations of lymphocytes and plasma cells and occasionally of epitheloid or histiocytic cells The lumen of these small ves els becomes narrowed or obliterated by a proliferation of its intimal layer, which becomes fibrotic and elastified (endarteritis obliterans) There may be localized or diffuse inflammatory changes consisting of granulation tissue and round

cells which form miliary gummata. The involved areas become replaced by scar tissue and by new vessels, both of which extend into the media.

2. **Changes in the Media.** The media has long been considered the site of the most prominent and most significant lesions,[28] whence the term "productive mesaortitis"[34] has been applied to this disease. It is probable that the medial lesions arise chiefly as a result of damage to the nutrient vasa vasorum and only in part through direct inflammatory changes in the media. The essential lesion is a necrosis of muscle and elastic tissue with the formation of scars markedly distorting the architecture of this vessel layer. These scars are often of a stellate form. Throughout the media there is an infiltration of round cells, plasma cells and fibroblasts. The thinning of the aortic wall and its loss of elasticity are essentially due to the destruction of the medial layer, while the wrinkled, puckered appearance is the result of the contraction of scar tissue extending from the adventitia to the intima.

3. **Intimal Changes.** There are intimal thickenings consisting of scar tissue and elastic elements. There may also be scattered inflammatory cells and capillaries which have extended from the media. Unless there is associated atherosclerosis, there is no lipoid or lime. However, atherosclerosis is frequently combined with syphilitic aortitis.

NON SYPHILITIC DISEASES OF THE AORTA

Inflammatory lesions of the aorta have been described by Siegmund[88] in a variety of infectious diseases, particularly scarlet fever, pharyngitis, subacute bacterial endocarditis. The aortic lesions of rheumatic fever have been described previously (p. 820). When extensive and severe, they may occasionally simulate syphilitic aortitis. Of special interest is the disease termed medionecrosis aortae idiopathica cystica.[■, 46] Microscopic examination reveals necrosis of the media with mucoid and cystic softening.[55] The lesions are situated in the ascending aorta and may lead to aneurysm of the sinus of Valsalva (p. 773) or to rupture of the aorta with dissecting aneurysm[8] (p. 555).

COMPLICATIONS OF SYPHILITIC AORTITIS

1. Coronary Artery Stenosis and Occlusion. The most intense syphilitic aortic lesions are situated so close to the mouths of the coronary vessels that these orifices are frequently implicated in the disease process. The incidence of severe narrowing or occlusion of the coronary ostia in luetic aortitis is at least 10 to 25 per cent.[61, 7, 50] By careful measurement with a calibrated metal cone inserted into the vessel openings Bruenn[4] demonstrated that narrowing occurred in 31 per cent of his cases of luetic aortitis. That the coronary ostia are not involved even more frequently is due to the fact that they are usually located within the sinuses of Valsalva, while the lesions of syphilitic aortitis tend to occur just above this level ("supravalvular sclerosis").[63] Not infrequently the coronary orifices have an anomalous origin higher up on the aorta, above the sinuses of Valsalva; in such instances they are almost always embedded within the syphilitic process. When the syphilitic process tends to extend downward so as to involve the commissures of the aortic valve, the incidence of severe coronary ostial stenosis or occlusion becomes very high. Thus coronary ostial stenosis and occlusion are frequently associated with aortic insufficiency, a point worth remembering in interpreting clinical symptoms.

The mouths of the coronary vessels become narrowed by encroachment of the raised intimal plaques upon their margins or by extension of the aortic syphilitic process into that portion of the coronary artery lying within the aortic wall, with subsequent contraction of resulting scar tissue. Stenosis of either one or both orifices may occur and virtually complete occlusion is not rare.[10] The syphilitic process rarely, if ever, extends beyond the aortic openings into the vessels themselves and then only for 1 to 2 cm.[71] But aneurysms of the proximal portion of the coronary arteries have been reported.[■]

Despite the relative frequency of syphilitic coronary stenosis or occlusion, resulting myocardial infarction is rare.[■, 64, 53] In a series of 185 cases of myocardial infarction only 3 were due to syphilitic coronary ostial occlusion.[7] These 3 cases were found in a series of 193 showing luetic aortitis at autopsy, 40 of them with coronary ostial stenosis. On the other hand, Love and Warner,[63] in a study of 10 cases with coronary ostial stenosis, found 8 with pronounced fibrosis of the myocardium and 4 with acute myocardial infarction. Rarely, sudden death in cases of luetic aortitis

is due to coronary embolism of one main artery arising in an associated atheromatous mural thrombus while the other coronary ostium is narrowed by the syphilitic process [77]

2 Syphilitic Aortic Insufficiency

Aortic insufficiency is the result of an extension of a luetic aortitis to the valve commissures and cusps and not of direct valvular involvement At postmortem examination aortic insufficiency is found in 20 to 35 per cent of cases of luetic aortitis [65]

The earliest, the most significant and the most diagnostic gross anatomic feature of luetic aortic insufficiency is the widening of the commissures of the aortic valves This is the chief factor in the production of insufficiency It is probably due to necrosis scarring and consequent dilatation of the aortic ring [29] The commissural spaces between the cusps may become as wide as 0 5 to 1 cm The free margin of the cusps may be everted rolled and retracted and the cusp itself stiffened and shortened This shortening and retraction is a second factor contributing to lack of coaptation of the cusps and resulting regurgitation Aortic stenosis does not occur in syphilis unless rheumatic valvulitis or calcification of the cusps is associated The combination of rheumatic and syphilitic aortic valvular disease has been documented [8] Bacterial endocarditis rarely complicates syphilitic aortic insufficiency unless there are associated rheumatic lesions (p 864)

Rarely there is an extension of the syphilitic aortitis by way of the annulus fibrosus not only to the aortic valve but also to the anterior mitral cusp[92] and to the septum fibrosum [90]

The heart itself becomes considerably enlarged due to dilatation and hypertrophy of the left ventricle especially its outflow tract

3 Aortic Aneurysm

Aortic aneurysm is a complication resulting from a severe and extensive luetic aortitis It has been found at autopsy in 10 to 30 per cent of cases of luetic aortitis In Martland's[63] series dealing with cases of sudden death it occurred in 38 per cent of the cases of cardiovascular syphilis The aortic wall becomes weakened as a result of the destruction of muscle and elastica in its medial layer When this is extensive and severe the continued blood pressure with its systolic accentuation serves gradually to dilate the vessel When there is a pronounced localized dilatation, a saccular aneurysm is formed

Saccular aneurysms may be multiple or single They most frequently involve the ascending aorta less often the arch, the descending and abdominal aorta in that order of incidence The aneurysmal sac may be filled with laminated thrombus which sometimes occludes a small perforation and on rare occasions is the origin of emboli The great danger of aneurysm is perforation, but most of the symptoms when present result from pressure on neighboring vital structures The pressure may be great enough to erode bone

SYPHILITIC MYOCARDITIS

Primary syphilitic disease of the myocardium was classified by Virchow[100] into the gummatous and fibrous varieties The fibrous lesions are non specific and there is doubt that they represent a distinct form of syphilitic myocarditis

Primary syphilitic myocarditis is uncommon and is confined to gummatous lesions There may be localized gummata or a diffuse gummatous myocarditis Sohval[91] was able to collect 97 authentic cases of cardiac gummata and only 7 of diffuse gummatous myocarditis The great majority of gummata occur at the base of the left ventricle and of the interventricular septum [95] Gummata situated in the interventricular septum may involve the bundle of His or one of its branches [95] A gumma may result in cardiac aneurysm may lead to rupture of a papillary muscle or of the heart wall or rarely occludes a valvular orifice

The diffuse gummatous myocarditis consists essentially of miliary or submiliary gummatous lesions with syphilitic granulation tissue and eventual scarring Although these lesions are rare they occasionally produce a distinct clinical picture one resembling acute myocardial infarction in a case reported by Reifenstein

CLINICAL FEATURES

UNCOMPLICATED SYPHILITIC AORTITIS

Symptoms

Syphilitic aortitis is an asymptomatic lesion The symptoms attributed to it are probably all due to its complications—coronary ostial stenosis aortic insufficiency or aneurysm—or to associated coronary atherosclerosis

Physical Signs

It is questionable whether there are distinctive physical signs of uncomplicated luetic aortitis. A *loud bell like or tambour like second aortic sound* (bruit de tabourka) has been described as characteristic. However, it may be absent and a similar sound is frequently heard in cases of hypertension and aortic atherosclerosis. Similarly a rough *aortic systolic murmur* may be due to syphilitic or atherosclerotic changes and dilatation of the ascending aorta. Both of these signs may be suggestive of syphilitic aortitis if they occur in subjects under 40 with a positive serologic reaction for syphilis and without hypertension or any other disease that may cause aortic dilatation.

CORONARY STENOSIS OR OCCLUSION

The clinical features of coronary ostial stenosis or occlusion sometimes cannot be separated from those of the commonly associated aortic insufficiency.

The slow progression of ostial stenosis permits the development of an extensive collateral circulation chiefly through extracardiac anastomoses.[11] Hence there are frequently no symptoms referable to coronary ostial stenosis even when the stenosis is severe and involves both main arteries.

As a rule severe coronary ostial stenosis is characterized by *angina pectoris* indistinguishable from that due to advanced coronary atherosclerosis except that it appears at a relatively earlier age. The clinical picture of acute myocardial infarction is seen rarely. *Sudden death* from ostial stenosis or atresia is not infrequent. By causing relative myocardial anoxia and not infrequently myocardial fibrosis, coronary ostial narrowing may induce or contribute to the development of heart failure, especially when the size and work of the heart are increased by a concomitant aortic insufficiency.

SYPHILITIC AORTIC INSUFFICIENCY

Cardiac pain and dyspnea are the most frequent symptoms associated with syphilitic aortic insufficiency. However, the cardiac pain is probably most often due to coronary ostial stenosis. In Bruenn's[6] series of 39 cases of the latter, 34 (87 per cent) revealed simultaneous aortic insufficiency. The infrequency of cardiac pain in rheumatic aortic insufficiency has been mentioned.

For relatively long periods cases of syphilitic aortic insufficiency may be well compensated. But even during this stage there may be palpitation, pounding in the ears or uncomfortable pulsations in the head and neck.

Left-sided heart failure probably develops not only because of the strain of the aortic valvular insufficiency but also because the development of coronary ostial stenosis prevents the increased blood flow required for the nutrition and work of the hypertrophied heart. This is analogous to the development of heart failure in compensated rheumatic aortic insufficiency when atherosclerosis narrows or occludes the coronary arteries. In syphilitic patients beyond the age of 50 coronary atherosclerosis as well as ostial stenosis may be an important factor in inducing both angina pectoris and congestive heart failure.

Paroxysmal dyspnea especially at night is an early and frequent symptom[6] ('syphilitic asthma'). Exertional dyspnea is also an early symptom of left ventricular failure in syphilitic aortic insufficiency. Sooner or later orthopnea, cough and weakness are associated. Attacks of acute pulmonary edema are not uncommon. Within a few years frank evidences of right sided failure also appear.

The physical signs of aortic insufficiency have been described (p 688).

ANEURYSM OF THE AORTA

Aneurysm of the aorta may remain asymptomatic for many years up to the final blow out. Symptoms occur as a result of pressure on neighboring organs or of perforation. The perforation is usually *into the pericardial or left pleural cavity*, the left bronchus, the esophagus or trachea, and occasionally into the right pleural cavity, right bronchus, the superior vena cava, pulmonary artery or externally.[4] Aneurysms of the sinus of Valsalva usually perforate into the right atrium and ventricle. Sudden death is common.

Aneurysm of the Ascending Aorta and the Aortic Arch

Aneurysms of the ascending aorta have been distinguished as "aneurysms of physical signs" in contrast to those of the arch which are termed "aneurysms of symptoms." The ascending aorta is most frequently involved. Since the ascending aorta is entirely within the pericardial sac, rupture occurs most frequently into that cavity. As it enlarges the

aneurysm usually extends anteriorly upward and to the right compressing the right bronchus and lung the superior vena cava and the second or third ribs to the right of the sternum Occasionally it produces pulmonary stenosis by compressing the pulmonary artery [7] It may attain enormous bulk and appear as a visible tumor in the first or second right interspace near the right sternoclavicular joint Occasionally such a visible tumor may be seen oozing blood from a superficial erosion and rarely the aneurysm ruptures externally

Aneurysms of the arch usually compress the trachea the esophagus the left bronchus the left recurrent laryngeal nerve and the sympathetic nerves When the aneurysm is essentially confined to the arch pressure on these structures is likely to produce symptoms quite early Patients with this lesion often first consult the laryngologist the gastroenterologist or the specialist in pulmonary disease

Symptoms *Chest pain* and *cough* are the commonest complaints The pain is often persistent and may be due to pressure of the aneurysmal sac on adjacent nerves or to the erosion of bone The cough which is dry at first and may have a brassy quality results from pressure on the trachea or main bronchus The brassy quality is ascribed to involvement of the recurrent laryngeal nerve Later in the disease the cough is associated with expectoration and more rarely with hemoptysis These are due to bronchostenosis and secondary infection with resulting atelectasis and bronchiectasis The clinical picture produced has been termed aneurysmal phthisis

Pulmonary and pleural symptoms may actually dominate the clinical picture of aortic aneurysm [8] Atelectasis bronchopneumonia abscess or bronchiectasis may arise not only from tracheal or bronchial compression but also from direct invasion of the lung by the aneurysm Tuberculosis may be associated Pleural complications arise as a result of rupture into the pleural cavity compression of the pulmonary or azygos veins or extension of pulmonary infection to the overlying pleura

Dyspnea is due to pressure on the trachea or on a bronchus Inspiratory stridor may develop *Hoarseness* results from paralysis of the left recurrent laryngeal nerve *Hemoptysis* may result from erosion of the trachea bronchus or pulmonary tissue or from bronchiectasis due to stenosis of a bronchus with secondary infection *Dysphagia* is due to partial obstruction of the esophagus When there is pain on swallowing it is probable that the esophageal mucosa has been eroded by the aneurysm Rarely pressure on the phrenic or sympathetic nerve produces symptoms such as hiccup diaphragmatic paralysis or unilateral absence of sweating of the face

Physical Signs The signs are essentially those of an expanding pulsating mediastinal tumor Inspection and palpation may reveal a pulsation in the anterior chest wall in the second or third right interspaces occasionally higher up or to the left Rarely a bloody tumor mass is visible on the chest wall There may be inequality of the pupils with dilatation of the right due to pressure on the cervical sympathetic chain Occasionally unilateral exophthalmos also results Suffusion of the face neck and upper extremities with cyanosis and edema may be produced by pressure on the great veins The edema and cyanosis may be localized to the right arm if the pressure is confined to the subclavian vein but this is rare

A systolic thrill and a *diastolic shock* may be palpated over the mass As a result of pressure of the aneurysm on the bronchi a *tracheal tug* synchronous with the heart beat may be felt as a downward pull at the thyroid or cricoid cartilage There may be an *inequality of pulses* usually the right one is diminished in amplitude delayed or obliterated by partial interclusion of the orifice of the innominate artery or aneurysmal involvement of that vessel itself There is a corresponding difference in blood pressure in the two arms

The heart is not enlarged as a result of aneurysm itself Systolic murmurs are often present over the aneurysm Diastolic murmurs are due to associated aortic insufficiency

Distinctive features permitting a clinical diagnosis appear when an aneurysm of the aorta perforates into the pulmonary artery[11] or into the superior vena cava [12] or when an aneurysm of the sinus of Valsalva perforates into the right atrium[4] or ventricle[11] (p 773) There is a loud continuous bruit with systolic accentuation and a palpable thrill as in arteriovenous fistulas Cardiac enlargement electrocardiographic signs of right ventricular strain and congestive heart failure appear quickly and usually lead to a rapid end Perforation into the superior vena cava is dis

closed also by cyanosis and edema of the face and neck, venous engorgement in the upper half of the body and pulsations in the cervical veins[67] In instances of perforation into the right atrium there may be visible double pulsations in the jugular veins resembling those of tricuspid stenosis The development of chronic cor pulmonale due to compression of the pulmonary artery by an aortic aneurysm has been reported[30]

Aneurysm of the Descending Aorta

Because of their location aneurysms of the descending aorta may reach immense size and may almost completely fill the left thoracic cavity before they produce symptoms either by pressure on neighboring organs or by perforation One is often surprised to find a huge thoracic mass on roentgenologic examination of a patient who has complained of few or no symptoms

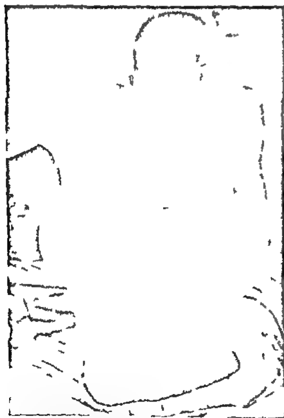


Fig 141 Huge syphilitic aneurysm of descending thoracic aorta visible on external surface of left posterior chest wall

As with aneurysms of the arch, the chief symptoms are chest pain dyspnea and cough Pleural effusion, hydrothorax and hemothorax rarely develop Dysphagia is an occasional symptom resulting from pressure on the esophagus An important sign of a large aneurysm of the descending aorta, and one often overlooked, is a visible pulsation on the posterior chest wall either below and to the left of the left scapula or somewhat higher in the interscapular region Rarely the aneurysm produces a visible pulsating mass in the left interscapular region (Fig 141)

Aneurysm of the Abdominal Aorta

Aneurysms of the abdominal aorta are generally considered to be predominantly atherosclerotic, syphilis being responsible for only 9 per cent in the series reported by Mills and Horton[70b] Atherosclerosis was responsible for 97 of 102 cases of abdominal aneurysm in the series reported by Estes[■] However, in other collected series of abdominal aneurysms in which there were more Negroes and somewhat younger individuals, syphilis was responsible for 50 to 80 per cent of the cases[47, 44] Syphilitic aneurysms occur predominantly in subjects below the age of 50 and almost exclusively below the age of 60[67] Atherosclerotic abdominal aneurysms occur predominantly in subjects beyond the age of 60 and almost never before 50 The syphilitic aneurysm usually occurs at the level of the celiac axis

The *commonest symptom* of syphilitic abdominal aneurysm is pain in the abdomen or back It may be paroxysmal, or constant and boring There may be root pains radiating from the back to the upper abdomen These and other symptoms result from erosion of the vertebrae, pressure on the spinal cord gastrointestinal tract ureter or other abdominal structures Death is usually caused by rupture of the sac into the peritoneal cavity gastrointestinal tract or retroperitoneal space Most abdominal aortic aneurysms are asymptomatic

Examination may reveal an expansile pulsating mass palpable thrill and audible bruit and occasionally a difference in the femoral pulsations Roentgenologic examination may disclose an abdominal mass with or without calcification and erosion of the anterior vertebral bodies from the eleventh thoracic to the second lumbar

GUMMATA OF THE HEART AND GUMMATOUS MYOCARDITIS

Cardiac gummata and gummatous myocarditis usually produce no clinical picture Rarely a gummatous aneurysm may per

with evidence of syphilitic aortic insufficiency who also suffers from angina pectoris Even under these circumstances the cardiac pain may be due to a concomitant coronary athero sclerosis especially in patients beyond the age of 50

cedures was reported positive in 75 to 95 per cent of the cases [13, 18] suggesting that in about 15 per cent of the cases of cardiovascular syphilis the serologic reaction may be nega tive However, this does not apply to more modern serologic tests and techniques for per



Fig 143 *A* Syphilitic aneurysm of arch of aorta presenting on left side
B Angiocardiogram of same Aneurysmal mass continuous with aorta and extending posteriorly (Arrow)

Diagnosis of Syphilitic Aortic Insufficiency

This diagnosis has been discussed in the chapter on aortic insufficiency (p 692) The syphilitic etiology of the valvular lesion is suggested by a positive Wassermann reaction absence of a cardiac murmur in childhood and absence of mitral stenosis and by the associa tion of angina pectoris The association of both syphilitic and rheumatic valvular disease has been noted [8]

Diagnosis of Syphilitic Aortic Aneurysm

This is essentially a radiologic problem (p 899) Occasionally there is a visible or palpable pul ating mass in the first or second right interspace or in the left scapular region The possibility of aortic aneurysm should be considered in any patient who has definitely had syphilis and who suffers from chest pain dyspnea cough especially a brassy cough hoarseness severe abdominal pain or pa ralysis of the recurrent laryngeal nerve The value of contrast angiocardiography has been mentioned

The Wassermann and Related Reactions in Cardiovascular Syphilis

The blood serologic reaction for syphilis as obtained by the Wassermann, or similar pro forming them It is probable that less than two or even less than one per cent of cases of cardiovascular syphilis have a negative sero logic reaction for syphilis The syphilitic na ture of cardiovascular lesions may be con firmed by the detection of treponemal im mobilizing antibodies in the blood even when the serologic reactions are negative [37] In 342 cases of cardiovascular syphilis in which the spinal fluid was studied by the Clinical Co-operative Group [18] significant abnormalities were found in 56 per cent Thus evidence of syphilis of the central nervous system should suggest a careful search for cardiovascular lues and vice versa

PROGNOSIS

In a large percentage of cases of cardio vascular syphilis evidence of this disease is a coincidental finding at autopsy Of 1040 in stances of cardiovascular syphilis studied at necropsy by Welty [101] the syphilitic lesion was a direct or important contributing cause of death in only 339 cases Rich and Webster [80] concluded that uncomplicated syphilitic aor titis carried a favorable prognosis as suggested by a relatively low death rate in a group of

of pneumoperitoneum injection of air into the colon, or by administering a Seidlitz powder Erosion of the upper lumbar vertebrae or of their transverse processes may be seen, especially in lateral views[6] In aneurysms of the thoracic aorta there may be concave erosions of the ribs or sternum as well as of the vertebrae Pleural or pulmonary abnormalities and rarely paralysis of one leaf of the diaphragm may be observed as a result of pressure of the aneurysm on neighboring structures

The roentgenologic findings in aortic insufficiency have been described elsewhere (p 689) Coronary ostial stenosis, per se and causes no radiologic abnormalities

Diagnosis of Uncomplicated Aortitis

This is a difficult diagnosis and its criteria are not well defined It may be considered when there is radiologic evidence of dilatation and/or calcification of the ascending aorta in a patient who is below the age of 40 has definitely had syphilis and is free from hypertension or rheumatic valvular disease[30] Accessory diagnostic findings may include a hollow or bell-like accentuated aortic second sound and an aortic systolic murmur In patients beyond the age of 40, but with all the other findings, the diagnosis may be arteriosclerosis or syphilitic aortitis



Fig 142 Syphilitic aneurysm of ascending aorta.

Angiocardiography

Angiocardiography has greatly facilitated the diagnosis of aortic aneurysms and especially their differentiation from mediastinal tumors[64 ** 12] (Fig 143) Merten et al have reported 9 cases of syphilitic aortic sinus aneurysms diagnosed during life by angiocardiography[70]

Definition of the exact site and extent of aneurysms of the aorta may be greatly facilitated by *aortography*[52]

Diagnosis of Syphilitic Coronary Ostial Stenosis or Occlusion

This may be considered in a patient with the above evidence of syphilitic aortitis, or

lessened and the duration of life was two to five times as great in the treated group as in the untreated

TREATMENT OF CARDIOVASCULAR SYPHILIS

Prophylaxis

Available data indicate that cardiovascular syphilis may be largely prevented by prompt case finding and adequate treatment and observation of early syphilis[23] Most of the data apply to treatment by arsenicals bismuth and mercurials prior to the widespread use of penicillin There is substantial evidence that the adequate early treatment of syphilis greatly reduces the incidence of syphilitic aortitis and its complications Treatment of early syphilis is now begun with the intramuscular administration, at multiple sites of 2 4 million units of a long acting penicillin Benzathine penicillin G fortified with procaine penicillin may be used, or procaine penicillin in oil with 2 per cent aluminum monostearate This is followed by four injections at four day intervals of 600 000 units of either of the latter preparations at each injection

Specific Therapy of Syphilitic Cardiovascular Disease

The aim of specific therapy in cardiovascular syphilis is to relieve the patient s symptoms and prolong his life without undue risk Specific therapy is given because cardiovascular syphilis denotes a persistently active inflammatory lesion which it is hoped can be controlled by antiluetic drugs In a pathologic study of 45 treated and untreated cases of syphilitic aortitis Webster and Reader[10] found persistent syphilitic inflammatory activity in all of 19 untreated cases and in only 3 of 19 adequately treated ones Although antisyphilitic therapy may control the active inflammation it cannot be expected to alter significantly certain irreversible lesions due to necrosis of muscle and elastic tissue and scar formation

Penicillin has now replaced all other drugs as the preferred therapeutic agent [4, ■] The preliminary administraton of bismuth or mercury designed to prevent a Jarisch Herxheimer reaction or therapeutic shock is no longer considered necessary or advantageous[22]

Uncomplicated syphilitic aortitis does not produce clinical symptoms and is not a definitely diagnosable entity The treatment of *syphilitic aortic insufficiency* and/or *coronary ostial stenosis* consists in the intramuscular administration of a total of 6 to 12 million units of penicillin[■] Six hundred thousand units of procaine penicillin in oil with 2 per cent aluminum monostearate or benzathine penicillin with procaine penicillin are administered daily for a period of 10 to 20 days or 600 000 units may be administered twice weekly for 5 to 10 weeks

This may be followed by relief of angina pectoris or nocturnal dyspnea and improved well being[2, ■] Except for mild fever in a few cases there are no significant reactions suggesting therapeutic shock[3]

Heart Failure and Angina Pectoris

Penicillin is given as described above and these complications are treated as described in Chapters 11 and 18

Surgical Treatment

The surgical treatment of aortic aneurysms has undergone remarkable advances and is now directed toward removal of the lesion and restoration of function[5] The treatment of aneurysms with polyethylene wrapping containing dicetyl phosphate to stimulate a protective fibrous tissue encasing[23] reinforcement of aneurysms with non absorbable polyvinyl sponge (Ivalon) electrothermic coagulation and the 'pack method of intrasaccular wiring[60] gave some favorable but inconstant results Thromboendarterectomy[101, 61, 16] has given some brilliant results in aneurysm of the terminal abdominal aorta which is usually of atherosclerotic etiology At the present time the preferred treatment of aortic aneurysm syphilitic or atherosclerotic is the excision of the aneurysm and suture of the aorta with graft replacement if necessary A major problem is the need to occlude the aorta during excision of the aneurysm graft replacement and suturing Below the level of the renal arteries the aorta may be occluded for adequate periods of one hour or more but occlusion of the aorta for aneurysms at higher levels for more than 20 minutes is usually associated with considerable risk Occasionally in syphilitic sacculated aneurysms a tangential resection is possible and the circulation in the major part of the lumen of the aorta need not be cut off[1] Recently there have been a number of reports of definitive cures of aortic aneurysm in all parts of the aorta with freeze dried graft replacement and restoration of continuity of the aorta[■, ■] Schafer and Hardin[84] reported the use of temporary polyethylene

elderly patients followed for an average period of seven years, and by the low incidence of the development of aortic insufficiency. Similarly the favorable course of uncomplicated syphilitic aortitis is suggested by the fact that this lesion is found post mortem in a large majority of persons with longstanding syphilis of whom only 5 to 10 per cent have had clinical evidence of the disease.

But even among those who eventually develop clinical evidence of cardiovascular syphilis there is an asymptomatic stage of considerable duration. According to the studies of syphilitic aortic insufficiency reported by McDermott[70] and associates this asymptomatic phase varies between two and ten years with an average of six years. Similarly Hubert[4] reported that of 137 patients with syphilitic aortitis 47 were completely free of symptoms after six and a half year; and Reader et al[78] found 16 of 27 patients with syphilitic aortic insufficiency who were asymptomatic and mostly working after five years of observation. The existence of a long asymptomatic period is suggested by the finding of virtually complete closure of both coronary ostia in the hearts of individuals who were asymptomatic and at work until a relatively brief period before death. It is also remarkable how often an aortic aneurysm reaches enormous size before it produces symptoms.

The further course and duration of life after the onset of symptoms is quite variable. It was formerly stated that this symptomatic phase was an ominously progressive one with death in one to three years. However, even Grant[38] found that the case fatality rate in syphilitic aortic insufficiency was only 64 per cent after ten years. Kampmeier and Coombs[49] in a study of the records of 163 patients with syphilitic aortic insufficiency, found that about 55 per cent died in the first three years after the onset of symptoms, 20 per cent died in three to twelve years, while the remainder were still alive, almost half of them, for an average period of ten years. The duration of the symptomatic phase in the group of patients with syphilitic aortic insufficiency studied by Reader et al[8] varied between two and fourteen years with an average of 5.6 years. In a series of 1020 patients with syphilitic aortic insufficiency followed in the New York and Johns Hopkins hospitals for a period of twenty years[103] 43 per cent of the New York group and 33 per cent of the patients at Johns Hopkins hospital survived ten years and 30 per cent of the former group and 20 per cent of the latter survived fifteen years. Twenty-one per cent of those over 60 at the time of diagnosis survived ten years. The survival time was much greater for those who were asymptomatic than for those with clinical symptoms at the time of diagnosis.

In general the outlook for uncomplicated syphilitic aortitis is much better than for cases with aortic insufficiency, aneurysm or coronary ostial stenosis. The outlook becomes distinctly more ominous when subjective symptoms appear, especially angina pectoris and those due to congestive heart failure or to aneurysmal compression of vital structures. In the presence of heart failure the mortality rate increases substantially and the duration of life averages two to three years. However 9 of 30 surviving patients studied by Reader et al[78] had suffered from congestive heart failure three to nine years previously and had responded to treatment. In the series reported by Webster et al[103] 28 per cent of those with angina pectoris and 6 per cent of those with heart failure survived for ten years. The outlook in cases of syphilitic aortic aneurysm is very poor once symptoms appear,[3] the average period of survival varying from 9 to 17 months with involvement of the ascending aorta, 6 to 9 months for the transverse aorta and 8 to 20 months for the descending aorta.[49] In cases of luetic aortitis complicated either by aneurysm, coronary ostial stenosis or aortic insufficiency there is always the danger of sudden death.[58, 67] The prognosis is worse in Negroes than in white patients. Patients engaged in occupations involving arduous physical exertion have a relatively unfavorable outlook.

Relation of Antisyphilitic Treatment to Prognosis

It is generally believed that adequate early treatment of syphilis greatly reduces the incidence of luetic aortitis and of its serious complications.[13, 101, 68] On the other hand there is less certainty as to the effectiveness of antisyphilitic therapy given after the clinical recognition of syphilitic aortitis. However, the studies of Padget and Moore[71] and the cooperative clinical report of Cole et al[18] suggested that after regular adequate treatment of cardiovascular syphilis with an arsenical and a heavy metal the mortality rate during the period of treatment was substantially

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Chapter 36

THE HEART IN INFECTIONS

Rheumatic fever and syphilis are the only infections responsible for common clinical forms of cardiovascular disease. These have been discussed in previous chapters. Almost all of the microorganisms are capable at times of producing a bacterial endocarditis and less commonly a purulent pericarditis and myocardial lesions. The endocarditis and pericarditis are due to local implantation and growth of microorganisms while the myocardial changes may be due either to the presence of these organisms or to toxic or metabolic disturbances or embolic vascular occlusions caused by the infection.

This chapter is concerned with the cardiac abnormalities associated with a variety of more or less specific infections or infectious diseases other than those mentioned above.[1] Diphtheria is the classic example of an infection accompanied by sufficient anatomic change in the heart to account for clinical heart disease. In almost all of the other infections evidence of cardiac involvement consists either of electrocardiographic changes which are usually non specific and transient or of relatively mild and non specific myocardial lesions which are found in fatal cases.

Clinically circulatory disturbances are uncommon or overshadowed by other manifestations of the infection. Acute circulatory failure (shock) is much more common than congestive heart failure. The latter is more likely to occur in patients with previous cardiac disease. Except for occasional instances of permanent heart block following diphtheria or of progressive heart failure due to myocardial involvement in schistosomiasis, chronic heart disease rarely results from any of the infections to be discussed. However, acute heart failure and unexpected deaths following certain infections have been attributed to myocardial involvement. During convalescence from many infectious diseases, dyspnea, precordial pain, extreme fatigability, symptoms resembling those of neurocirculatory asthenia are not infrequent. It is improbable that they are due to myocardial disease. Recent stress on microscopic lesions in fatal cases of acute infectious diseases (other than rheumatic fever, syphilis or diphtheria) and on the frequency of electrocardiographic changes tends to exaggerate the importance of myocardial involvement in these diseases.

THE HEART IN DIPHTHERIA

Incidence of Acute Myocarditis

Acute myocarditis is said to occur in 10 to 25 per cent of cases of diphtheria, the incidence being particularly high in epidemics with severe forms of the disease. But diphtheritic myocarditis is very rare in the United States because of the extreme reduction in the incidence of diphtheria and the early effective treatment. Myocarditis may complicate cutaneous[18] as well as faucial diphtheria and is often associated with cranial nerve involvement. Wesselhoeft[20] noted a mortality rate of 11.3 per cent in a series of 15,490 cases of diphtheria, 59.4 per cent of these deaths were due to acute myocarditis.

Pathogenesis of Cardiovascular Disturbances

The circulatory disturbances in cases of diphtheria are due to the action of the exotoxin of the Klebs-Loeffler bacillus and not to the microorganism itself. The cardiac damage observed microscopically is likewise due to toxic effects on the muscle fibers, but the myocardial changes have been attributed also to toxic damage to the smallest coronary vessels with secondary myocardial anoxia.[14]

Pathology

Fahr[13] described three types of change in the heart: (1) fatty degeneration, (2) myolysis and (3) interstitial inflammation. Severe fatty hyaline and other degenerative or necrotic changes in the muscle fibers occur near the end of the first and beginning of the second week.[13, 3, 16] Interstitial changes usually

represent a secondary reaction to the parenchymal damage and appear in the latter half of the second week of the disease[26] But interstitial myocarditis without parenchymal change has also been described[27] The interstitial inflammatory alterations consist of edema and focal or diffuse infiltrations of lymphocytes neutrophilic and eosinophilic leukocytes monocytes and fibroblasts The so-called toxic myolysis[12] denotes a solution of the muscle fibers the sarcolemma is seen to surround a clear or hyaline substance without cross striations or nuclei Reparative changes appearing during the second week are represented by fibroblasts granulation tissue young collagen fibers and later by well formed scars Scar formation is usually well established after three weeks[12]

CLINICAL FEATURES

Early Circulatory Disturbances

Acute circulatory failure may occur in the first few days Electrocardiographic changes are usually absent Tachycardia occurs commonly Cough and cyanosis are usually due to respiratory obstruction by a diphtheritic membrane and not to myocardial failure

Late (Convalescent) Cardiovascular Abnormalities

Near the end of the first and during the second week cardiovascular abnormalities may be due to an acute myocarditis Occasionally severe cardiovascular symptoms appear four to seven weeks after the onset of diphtheria particularly in cases of cutaneous diphtheria[13] The clinical evidences of diphtheritic myocarditis are (1) electrocardiographic changes (2) cardiac signs (3) cardiac shock and more rarely (4) congestive heart failure

Electrocardiographic Changes. Electrocardiographic abnormalities are usually the earliest evidence of acute myocarditis and have been noted by Burkhardt et al[8] in 20 per cent of 140 cases by Altschuler et al[2] in 24 per cent of 600 cases and even more frequently by other observers[3 5]

The earliest change is a mild saucer shaped depression of the ST segment[4] and by far the commonest change is a lowering or inversion of the T wave in two or more leads[2]

Although conduction disturbances are much less frequent they are more distinctive of diphtheritic myocarditis and denote a serious prognosis Complete heart block has been considered characteristic but prolongation of the P R interval and more severe grades of partial heart block have been described[6 8] Intraventricular conduction disturbances including bundle branch block occur as commonly as complete heart block[11 1] Since complete heart block in diphtheria may be associated with a normal or rapid ventricular rate as well as with the more usual bradycardia, it may be overlooked on physical examination As a rule the heart block persists less than a week Complete heart block is usually ominous All of the 11 patients with this disturbance in the series of Burkhardt et al[8] succumbed in Begg s[6] series 8 of 12 patients with complete heart block died Bundle branch block is similarly serious there was a fatal outcome in 4 of 6 cases observed by Begg[6] and in all 4 of those recorded by Cookson[11]

If the patient recovers the electrocardiographic abnormalities including the severe conduction disturbances usually disappear rapidly However bundle branch block or complete heart block said to have followed diphtheria has been reported as still present after intervals of between five and forty two years[18 6 20]

Among other electrocardiographic changes recorded in cases of diphtheria are sinus tachycardia or bradycardia transient extrasystoles and nodal rhythm paroxysmal tachycardias[6] atrial fibrillation following complete heart block,[24] atrial flutter with varying grades of heart block,[4] prolongation of the Q T interval[7] and postdiphtheritic ventricular fibrillation with recovery[17]

Cardiac Signs Tachycardia is usually present in the first week of diphtheria even when there is no myocardial involvement With the development of acute myocarditis there is often a gradual or sharp reduction in the heart rate which may result in a mild or pronounced *bradycardia* In the third week of the disease tachycardia may reappear in cases with myocarditis Heart rates below 40 indicate the presence of complete heart block but the latter may be associated with a normal heart rate or a slight tachycardia *Gallop rhythm* is an important sign of diphtheritic myocarditis with extensive myocardial damage and heart failure Occasionally there is *cardiac enlargement* Weakness of the first heart sound tic tac rhythm (embryocardia) and systolic murmurs have also been noted as evidence of myocarditis

Cardiac Shock

Extensive myocardial damage may result in a sharp diminution in cardiac output and produce the clinical picture of shock. The clinical syndrome of cardiac shock usually appears in the second week of the disease and is sometimes heralded by striking pallor, vomiting and abdominal pain. A grayish cyanosis, coldness of the extremities, complete apathy, collapse of the peripheral veins and a sharp fall in blood pressure are prominent features. Tachycardia and a small thready pulse are usual in shock but in the presence of complete heart block the pulse rate may be slow or relatively normal. Not infrequently the clinical picture of shock may result from peripheral circulatory failure rather than from cardiac damage.

Congestive Heart Failure. A moderate degree of congestive heart failure is usually associated with but overshadowed by the evidences of cardiac shock. The characteristic clinical picture of left- and right-sided failure with signs and symptoms of pulmonary congestion and of peripheral edema and venous engorgement, occurs very uncommonly. This is probably due to the fact that either the patient succumbs from cardiac shock if the damage to the heart is sufficiently severe or the myocardial changes regress if the patient survives. But I have seen a six year old boy who died with the typical clinical picture of congestive heart failure three weeks after the onset of an attack of diphtheria which was undiagnosed and untreated until his admission to the hospital just before death. His electrocardiogram showed severe changes in the QRS complex including low voltage notching, slurring W shape in lead I and a deep Q_4. The T waves were low and semi-inverted. The electrocardiographic appearance was that of a recent myocardial infarction.

Other Circulatory Abnormalities

Occasionally *intracardiac thrombi* are formed, especially in cases with subendocardial myocardial hemorrhage and inflammation which extend to the endocardium. These thrombi may be the source of emboli which produce isolated or repeated infarctions of the brain or lungs. Hemiplegia, cough and hemoptysis with pulmonary signs, and gangrene of an extremity have been observed.[9, 31]

Patients with complete heart block rarely suffer from epileptiform convulsions, syncope or other symptoms of the *Adams-Stokes syndrome*. Attacks of *angina pectoris* occur rarely. Late in the convalescent period, about the fourth to sixth week, patients may present a persistent tachycardia or a tachycardia induced by slight effort or at the end of the day. A *bacterial (diphtheritic) endocarditis* due to the Klebs-Loeffler bacillus occurs rarely.

DIAGNOSIS

The presence of acute myocarditis in a patient with diphtheria is indicated first by severe electrocardiographic abnormalities, especially complete heart block or bundle branch block. Clinically, a weakening or splitting of the first sound at the apex, gallop rhythm and cardiac enlargement usually denote an acute myocarditis. A severe myocarditis is revealed by the development of cardiac shock or congestive heart failure, usually in the second or third week of the disease.

PROGNOSIS

Acute myocarditis is a serious complication of diphtheria, accounting for most of the deaths in this disease after the first week. According to Place[3] and others[16, 4] the mortality rate varies between 50 and 60 per cent being almost 100 per cent in children between the ages of one and two, 50 per cent between two and ten, and 25 per cent among adults. In fatal cases death occurs usually in the first two weeks of the disease but occasionally later.

A poor prognosis is indicated by electrocardiographic evidence of heart block or bundle branch block and by certain clinical manifestations, such as a sudden reduction in heart rate with resulting bradycardia, persistent and marked tachycardia in the second or third week of the disease, gallop rhythm and especially the development of cardiac shock with or without congestive heart failure.

That diphtheritic myocarditis may lead to permanent fibrosis which predisposes to cardiac enlargement and congestive heart failure much later in life has been suggested but remains unproven.[27] On the other hand certain conduction disturbances developing during the active myocarditis may persist for many months or years or even permanently (p 388). Thompson, Golden and White[8] examined 100 persons who had had severe or moderately severe diphtheria from fifteen to twenty years previously; in none was there evidence of atrioventricular or intraventricular

block They concluded that there is no proof that diphtheria contributes to the later development of heart block

TREATMENT

The treatment of diphtheritic myocarditis is that of the underlying diphtheria The early and adequate use of diphtheria antitoxin and penicillin is most important Bed rest should be longer than in the uncomplicated case of diphtheria The treatment of shock is similar to that discussed under myocardial infarction (p 562)

SCARLET FEVER

Confusion as to the occurrence of heart disease during scarlet fever has arisen from a failure to distinguish three forms of cardiac involvement

1 Bacterial (hemolytic streptococcal) endocarditis pericarditis or myocarditis

2 Rheumatic heart disease (endo- myo-, pericarditis)

3 Benign (non bacterial) carditis due to scarlet fever per se

Bacterial or Suppurative Cardiac Disease

Rarely there is an acute bacterial endocarditis or a suppurative pericarditis secondary to hemolytic streptococcal bacteremia The latter arises from suppurative complications such as a purulent arthritis osteomyelitis or more often a sinus thrombosis following otitis media and mastoiditis In addition to endocarditis or pericarditis there may be foci of necrosis in the myocardium or abscesses of miliary or larger size Embolic gangrene of an extremity associated with scarlet fever[39] is suggestive of a complicating acute streptococcal endocarditis

Scarlet Fever and Rheumatic Heart Disease

This relationship was discussed above (p 808) where it was concluded that scarlet fever like other hemolytic streptococcal infections could precipitate or reactivate rheumatic fever with subsequent rheumatic heart disease When chronic cardiovascular heart disease follows scarlet fever the pathologic lesions are identical with those of rheumatic heart disease

It is well known that scarlet fever may be followed shortly by arthritis which in turn may be complicated by endocarditis and chronic heart disease It is essential to distinguish two forms of non suppurative arthritis associated with scarlet fever First there is a true scarlatinal synovitis or arthritis such as occurs with other infections which is unrelated to rheumatic fever and is never followed by heart disease Second there may appear a true rheumatic polyarthritis usually in subjects with preexisting rheumatic heart disease in whom rheumatic infection is reactivated by the scarlet fever In general, benign scarlatinal arthritis occurs earlier usually between the fourth and tenth days of the disease rheumatic arthritis usually appears in the third or fourth week of the disease The benign arthritis, like other forms of infectious arthritis frequently involves the joints of the fingers and hands while these joints are uncommonly affected in rheumatic fever

SCARLATINAL (BENIGN) CARDITIS

This refers to non specific electrocardiographic clinical and pathologic changes similar to those observed in many other infectious diseases Such cardiac complications were noted in 106 (6 per cent) of 1770 cases studied by Rosenbaum[37] A definite verrucous endocarditis with permanent valvular damage has been reported rarely[40] but the rheumatic or bacterial origin of the verrucae must be considered Similarly, occasional instances of pericarditis attributed directly to scarlet fever were probably due to an activation of rheumatic fever or to a complicating streptococcal bacteremia Scarlet fever does not appear to produce a chronic form of heart disease independent of rheumatic or bacterial (suppurative) complications

Pathology

As a rule there are no significant myocardial lesions or only mild degenerative changes such as cloudy swelling of the muscle fibers Occasionally there are mild focal or diffuse interstitial cellular infiltrations of lymphocytes and plasma cells and less often of neutrophilic or eosinophilic leukocytes But some observers have claimed that the myocardial lesions of scarlet fever are more severe and occur frequently[3, 35] Great care is necessary not to misinterpret the myocardial lesions of diphtheria for the latter disease may occur coincidentally in about one fifth of the cases of scarlet fever and may be unrecognized clinically

Clinical Features

The so-called scarlet fever heart has been diagnosed near the end of the first week of the disease or during convalescence[35] on the

Cardiac Shock

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PROGNOSIS

Acute myocarditis is a serious complication of diphtheria, accounting for most of the deaths in this disease after the first week. According to Place[3] and others[14, 31] the mortality rate varies between 50 and 60 per cent, being almost 100 per cent in children between the ages of one and two, 50 per cent between two and ten, and 25 per cent among adults. In fatal cases death occurs usually in the first two weeks of the disease but occasionally later.

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That diphtheritic myocarditis may lead to permanent fibrosis which predisposes to cardiac enlargement and congestive heart failure much later in life has been suggested but remains unproven.[7] On the other hand certain conduction disturbances developing during the active myocarditis may persist for many months or years or even permanently (p. 388). Thompson, Golden and White[9] examined 100 persons who had had severe or moderately severe diphtheria from fifteen to twenty years previously; in none was there evidence of atrioventricular or intraventricular

ally, as a rule in elderly patients and those with underlying heart disease The electrocardiographic changes occur chiefly after defervescence, but also before and during the crisis

Size of the Heart

The size of the heart was studied by Levy[49] by means of successive roentgenograms during the course of the disease He reported a significant enlargement in 61 9 per cent of 71 cases It is often difficult to exclude the factor of abdominal distention with elevation of the diaphragm in modifying the position and apparent size of the cardiac silhouette Associated cardiac failure and sodium water retention in the course of lobar pneumonia may account for definite enlargement of the heart in some cases

Circulatory Measurements

The *blood pressure* remains fairly constant but usually falls sharply if acute circulatory failure develops[5]

The *venous pressure* is usually normal but may be elevated especially in persons with preexistent heart disease and congestive heart failure[47]

The *circulation time* is usually normal but was prolonged in about 10 per cent of 75 cases studied by Hitzig et al[47] and in about 25 per cent of those observed by Sigler et al[44] The prolonged circulation times were encountered more often in those who succumbed than in those who recovered and in those beyond the age of 45 than in those below that age

The *circulating blood volume* was found to be normal in cases without circulatory failure[47]

The *cardiac output* was found to be increased during the febrile stage below normal after the crisis and back to normal only after one to three weeks[48]

Congestive Heart Failure and Acute Circulatory Failure

Acute circulatory failure (shock) occurs most often in very toxic cases of lobar pneumonia especially those associated with bacteremia and consolidation of multiple lobes It usually occurs at the height of the disease just before the crisis occasionally earlier and less frequently after the crisis The clinical picture is that of apathy or restlessness and disorientation weak rapid pulse cold extremities grayish cyanosis collapsed peripheral veins and a terminal drop in blood pressure in fatal cases Although the occurrence of shock in pneumonia is of ominous significance recovery is not rare

Congestive heart failure is less common than shock, it usually occurs only in elderly patients and those with preexistent organic heart disease Left sided heart failure is difficult to recognize in the presence of pneumonia but the diagnosis may be aided by finding a prolonged circulation time Pulmonary edema may occur in severe and fatal cases of pneumonia due to toxic damage and increased permeability of the pulmonary capillaries In such instances of pulmonary edema not due to left sided heart failure the circulation time is normal[47] Right sided heart failure is revealed by venous congestion increased venous pressure and moderate hepatic enlargement but peripheral edema is usually absent or occult

Treatment of Circulatory Complications

The most important measures are the early and adequate use of chemotherapy and antibiotics to control the underlying infection Theoretical considerations and clinical results[49] suggest that digitalis should not be administered in uncomplicated cases of lobar pneumonia However it should be given if there is definite evidence of congestive heart failure with or without atrial fibrillation

Atypical Pneumonia

In a series of 321 cases of atypical pneumonia 3 7 per cent revealed changes in the RST segments flattening or inversion of T waves and prolongation of the P R interval or of the QRS complex in the electrocardiogram[51] The changes have been interpreted as evidence of myocardial involvement, in some instances they are identical with those described under acute pericarditis

INFLUENZA

The influenza bacillus causes occasional cases of *bacterial endocarditis* Rarely it may produce a fibrinous or purulent *pericarditis*

Myocardial changes are uncommon and mild They consist of cloudy swelling of the muscle fibers and focal or diffuse collections of round cells and histiocytes[61] Rarely there are more severe destructive changes of muscle fibers[62]

Cardiovascular disturbances are uncommon Acute circulatory failure may occur in toxic cases and rarely congestive heart failure[59] During convalescence weakness precordial pain, palpitation and dyspnea are common

Electrocardiographic Changes A prolongation of the P-R interval is not uncommon and occasionally there is more severe partial heart block [62] Complete heart block has also been reported This may be associated with Adams Stokes syndrome and may disappear after a few days [illegible]

Sinus bradycardia is common during convalescence Extrasystoles, sinoatrial block, wandering pacemaker, nodal rhythm, tall notched P waves and abnormalities of the T wave and S T interval have also been observed occasionally [60] Occasional death from acute coronary thrombosis has been noted in young adults following an attack of influenza

TYPHOID FEVER

A bacterial endocarditis or pericarditis due to Eberth's bacillus is extremely rare Myocardial lesions are infrequent mild and non specific

Pathology of the Myocardium

Recent studies have disclosed merely cloudy swelling of the muscle fibers, a mild degenerative change seen in many infections Very infrequently there is an interstitial myocarditis with an infiltration of round cells and polymorphonuclear leukocytes

Electrocardiographic Abnormalities

Electrocardiographic abnormalities occur in the majority of cases of typhoid fever either during the acute illness or during convalescence [illegible] [illegible] [67] The commonest changes are *flat, diphasic or inverted T waves* in two or more leads These abnormalities usually appear in the third or fourth week of the illness and return to normal one to three weeks after the onset of convalescence In 23 of 35 patients with T wave abnormalities Rachmilewitz and Braun[67] observed [illegible] rapid normalization of the electrocardiogram following the administration of niacin

A prolongation of the P R interval has been noted by some observers, especially during convalescence, but this was found only once in Mainzer's[65] series of 106 cases Occasionally complete heart block has been recorded [64]

Relative bradycardia is characteristic of the febrile stage True bradycardia and sinus arrhythmia are common during convalescence, but tachycardia may appear in the third to fifth week of the illness as an evidence of myocarditis, effort syndrome or of complications such as intestinal hemorrhage or perforation

Clinical Circulatory Disturbances

Acute circulatory failure (shock) occurs occasionally as a result of toxemia, dehydration or hemorrhage I have seen a boy, aged 15, admitted on the fifth day of his illness with evidence of extreme dehydration and shock The heart rate was 140, the pulse thready, the heart sounds weak and tic tac in quality The blood pressure was too low to measure accurately He recovered after transfusions

Congestive heart failure [illegible] extremely rare except in cases of preexisting heart disease In a woman of 25 whom I observed, tachycardia gallop rhythm, cardiac enlargement and hepatomegaly were noted five weeks after the onset of typhoid fever The electrocardiogram revealed inversion of the T wave in leads I, II and IV These changes disappeared only after three months, while the cardiac abnormalities did not disappear until four months after they were first noted

MENINGOCOCCUS INFECTIONS

The meningococcus may produce an *acute or subacute bacterial endocarditis* with or without meningitis

Pericarditis also may result from a meningococcemia and is usually associated with meningitis But in the case reported by Orgain and Poston [illegible] meningococcus pericarditis with a large effusion and tamponade of the heart occurred without a history of preceding meningococcemia or meningitis Herrick[70] observed pericarditis 12 times among 280 cases of meningococcus meningitis, 6 were fibrinous and 6 were associated with purulent or seropurulent effusions of 30 to 640 cc Conklin[68] reported a case in which there was a turbid effusion of 1500 cc Recovery may occur spontaneously or with the aid of pericardial paracentesis, sulfonamides and penicillin

Myocarditis was observed post mortem in 111 of 256 cases of meningococcemia [69] There are microscopic foci of interstitial and perivascular cellular infiltrations Occasionally there are microscopic or macroscopic abscesses with destruction of muscle fibers [72] [73] Intracellular and extracellular gram negative diplococci have been demonstrated

Isolated electrocardiographic [illegible]hanges have been noted In one case of prolonged meningococcemia without meningitis which I observed there was a transient prolongation of the P R interval to 0 24 second Distinct R T eleva

tions should suggest the presence of pericarditis

UNDULANT FEVER

Infections with brucella organisms rarely involve the heart a *bacterial endocarditis* being the most frequent cardiac complication (p 876) This occurred in 1 per cent of 300 cases studied by Hardy [77]

Pericarditis with effusion also occurs rarely and was noted twice by Hughes[78] and once in association with endocarditis by Hardy [77]

The myocardium may disclose an infiltration of small and large round cells and moderate cloudy swelling and granular degeneration of the myocardial fibers [75]

Electrocardiographic abnormalities found by Rubegni[79] included elevations or depressions of the RS T interval and low isoelectric or inverted T waves Usually the electrocardiographic changes revert rapidly to normal but I have seen inverted T waves persist for two months Atrial fibrillation has been noted [74] Acute circulatory failure occurs occasionally [76]

TUBERCULOSIS

Tuberculosis may be associated with extensive pulmonary changes causing increased pulmonary vascular resistance pulmonary hypertension and chronic cor pulmonale (Chapter 39)

Tuberculosis may involve the heart directly most often causing a tuberculous pericarditis with effusion (p 602) with or without compression of the heart (p 609)

Tuberculosis of the myocardium is rare although more than 200 cases have been reported [85] Custer and Charr[81] discovered an incidence of 0 44 per cent in about 15 000 cases of tuberculosis The myocardium is most often involved by an extension of contiguous pericardial lesions but occasionally by infection from the blood stream Three types of lesions have been described the miliary the large nodular and the diffusely infiltrating [83] The latter may cause widespread destruction as in the case of Bellet et al ,[illegible] in which it extended from the pericardium through the ventricular myocardium to reach the endocardium The large nodular or the infiltrating lesions may rupture into the cardiac cavity and cause a disseminated tuberculosis The infiltrating type may involve the atria and cause atrial fibrillation The large nodular lesions are usually found in the atria and may form tumor like nodules termed tuberculoma [illegible] They may be asymptomatic or cause obstruction to blood flow

Myocardial tuberculosis is usually asymptomatic Involvement of the atria may result occasionally in atrial premature beats atrial flutter or fibrillation [88] These arrhythmias in a patient with tuberculosis especially tuberculous pericarditis should suggest atrial involvement [8] Paroxysmal ventricular tachycardia has been recorded as occurring with myocardial tuberculosis [87] Congestive heart failure was attributed to extensive myocardial scarring secondary to tuberculous myocarditis in one of Wilbur s[89] cases

Endocardial tuberculosis is the rarest form of cardiac tuberculosis The endocardium may be involved by extension of pericardial or myocardial lesions or as part of a disseminated miliary tuberculosis Rarely isolated tuberculous valvular endocarditis has been reported [84]

ACTINOMYCOSIS

Actinomycosis rarely affects the heart As a rule the pericardium is affected by extension of neighboring lesions in the lungs, mediastinum or other thoracic structures [6] Very rarely the myocardium is invaded by way of the general blood stream or coronary arteries and occasionally by extension of pericardial actinomycosis Bacterial endocarditis due to Actinomyces bovis has been reported the valvular lesion being the only lesion in the heart

The pericardium reveals necrotizing suppurative and sclerotic lesions [90] There is usually a seropurulent yellowish cloudy fluid which is occasionally hemorrhagic The pericardial layers become thickened and adherent The fibrocaseous material extends to the myocardium and even to the endocardium producing necrosis and abscesses and masses of various sizes These masses may obstruct a valvular orifice,[91] or may break into the cardiac cavities or coronary veins and cause a dissemination of actinomycosis

Despite amazingly extensive lesions there may be no clinical symptoms referable to the heart As a rule the cardiac symptoms when present are overshadowed by those referable to the primary disease Involvement of the heart may be suspected in a patient with actinomycosis if there are evidences of pericarditis, arrhythmias or congestive heart fail-

ure In Uhr's[93] case the entire clinical picture of bacterial endocarditis was due to the valvular lesion

VIRUS INFECTIONS

Measles

Significant electrocardiographic changes were reported in 20 of 106 patients with measles T wave abnormalities and prolonged atrioventricular conduction was observed [105]

Infectious Hepatitis

Electrocardiographic changes consisting of T wave depressions were found in 9 of 11 cases studied by Dehn et al [96] Christiansen and Warburg[97] described a depression of heart rate and negative or isoelectric T waves in leads II and III Foci of myocardial necrosis and diffuse serous inflammation have been described [104a]

Infectious Mononucleosis

Clinical electrocardiographic and pathologic evidence of cardiac involvement in infectious mononucleosis has been noted by Houck [107] The electrocardiogram disclosed low voltage of the QRS and T waves in 4 to 100 cases and in 2 of these the T wave was inverted [101] In one patient there was a pericardial rub and in another a pericardial effusion Abnormal electrocardiograms were observed in 23 per cent of 223 patients with infectious mononucleosis [118] In necropsied cases sparse collections of mononuclear cells and lymphocytes have been noted about blood vessels or elsewhere in interstitial tissue [98]

Influenza A

Two cases of non bacterial myocarditis in one of which death resulted from heart failure were recorded by Finland et al [103] Acute congestive heart failure was reported by Borden [95] There may be necrosis of muscle fibers with extensive cellular infiltrations

Epidemic Parotitis (Mumps)

T wave changes and a prolongation of the P R interval were described by Wendkos and Noll [120] Rosenberg[113] observed electrocardiographic abnormalities in 15 per cent of 104 cases usually during the fifth to tenth day of the illness There were inversion of T waves, elevation of the ST in CF_4, biphasic or inverted P waves prolongation of the P R interval and 1 case each of partial and complete heart block Bengtsson and Ohrndal[94] observed electrocardiographic changes in 4 4 per cent of 564 cases of mumps These consisted of S T segment depressions low or negative T waves and atrioventricular block In a case reported by Felknor and Pullen[102] there was clinical evidence of congestive heart failure including gallop rhythm, tachycardia enlargement of the liver and râles at the bases of the lungs

Acute Anterior Poliomyelitis

Myocarditis has been found in 40 to 90 per cent of necropsied cases of poliomyelitis [117, 119] Electrocardiographic changes were found in 14 per cent of 467 patients [104] and in 84 of 181 patients in another series [109] They occur early and may persist several weeks Prolongation of the P-R interval ST segment deviations flat or inverted T waves and prolonged Q T interval are the abnormalities encountered [illegible] [110, 111] Hypertension may develop with bulbar poliomyelitis Pulmonary edema may be due to cerebral disease or left heart failure Bulbar poliomyelitis is commonly associated with a syndrome of cardiovascular collapse due to involvement of the medulla and an interstitial myocarditis [106] Absence of this syndrome in cases of spinal paralysis despite the presence of myocarditis, indicates that the clinical picture is due chiefly or exclusively to disease of the medulla The syndrome occurs within one or two days after the onset of bulbar paralysis, and is characterized by high temperature, anxiety, tachycardia and shock Pulmonary edema is a common terminal feature The inhalation or insufflation of 100 per cent oxygen may correct arterial anoxemia and shock and reverse the downhill clinical course [99a] Pathologically microscopic perivascular and interstitial cellular infiltration of lymphocytes, plasma cells and especially neutrophilic polymorphonuclear leukocytes and edema are occasionally observed [116, 99, 100, 112, 108] Isolation of the poliomyelitis virus from the heart in fatal cases of poliomyelitis has been reported [108]

Other Viral Diseases

Virus myocarditis has also been reported in connection with Coxsackie B virus [illegible] varicella psittacosis, dengue epidemic encephalitis and yellow fever [114] In three cases of encephalitis with electrocardiographic changes indicating myocardial damage, the disease was attributed to viruses and was interpreted as an entity similar to encephalo myocarditis observed in animals [115]

RICKETTSIAL DISEASES

Typhus Fever

Gore and Saphir[121] found pathologic evidence of myocarditis in 23 of 48 fatal cases of epidemic typhus and in 9 to 19 cases of Rocky Mountain spotted fever Herzog and Rodriguez[1 2] described (1) vascular changes (2) perivascular and subendocardial interstitial nodules and (3) diffuse interstitial inflammatory changes in 97 per cent of 103 hearts in an epidemic of typhus fever in Chile Capillary and precapillary vessels undergo endothelial proliferation occasional necrosis inflammation of the vessel wall occasional mural thrombosis and a pericapillaritis

Acute circulatory failure (shock) may occur in the middle of the second week or earlier in toxic cases[1 4] Gallop rhythm is occasionally heard but frank congestive heart failure is rare

Electrocardiogram Low isoelectric diphasic or inverted T waves were observed in 72 per cent of 85 cases and a prolongation of the P R interval in 48 per cent[1 8] In one case there was a right bundle branch block and at post mortem examination the heart presented multiple small infarcts due to necrotizing thromboarteritis of the small vessels In patients recovering from typhus fever the electrocardiographic abnormalities disappear and there is no chronic heart disease

Scrub Typhus (Tsutsugamushi Fever)

Pathologic evidence of myocarditis was found by Gore and Saphir[121] in all of 227 cases of scrub typhus Endothelial proliferation and perivascular infiltrations of round cells and necrosis of muscle fibers are the commonest findings[1 4] Minor electrocardiographic abnormalities include ST segment depression or elevation and low T waves[1 2] In 5 or 6 patients with cardiac decompensation Hollander[1 3] found low amplitude of the QRS complexes

TRICHINOSIS

Trichinosis is not infrequently associated with pathologic and electrocardiographic evidence of myocarditis[125]

Pathology There are interstitial and perivascular collections of eosinophilic and neutrophilic leukocytes lymphocytes and occasional mononuclear and plasma cells associated with focal necrosis of the muscle fibers[130]

The Trichinella spiralis was observed in the myocardium in the case of Zenker[137] and in one of Terry and Work[134] In Spink's[135] case the larvae were found after digestion of the heart muscle with artificial gastric juice although not demonstrable on histologic examination As a rule however the larvae are not observed in the heart It is believed on experimental grounds that the myocardial changes are caused by the presence of the trichinella larvae but that they do not become encysted in the heart and either die early or migrate elsewhere[129 131] Therefore they are not observed if death occurs after the first week or two The myocarditis may represent a fixed tissue reaction to antigenic factors of T spiralis

Clinical evidence of myocarditis is usually absent Occasionally there is acute circulatory failure (shock) I have twice noted gallop rhythm In these two cases there were other evidences of congestive heart failure including dyspnea venous engorgement and peripheral edema Terry and Work[134] reported a verified case of trichinosis myocarditis which was mistaken for rheumatic fever because of the combination of arthritis fever epistaxis and a prolonged P R interval in the electrocardiogram

Electrocardiographic changes were observed in 2 of 44 cases of Beecher and Amidon[128] in 6 of 18 by Spink[135] in one third of the cases studied by Cushing[1 7] and in 21 per cent of 114 cases observed by Solarz[136] Flattening or inversion of the T waves occurs in two or more limb leads especially lead II or leads I and II and in the precordial leads Occasionally upward convexity of the RS T segment and cove plane type of T inversion simulate the changes seen in acute myocardial infarction[127 132] A prolongation of the P R interval low voltage of the QRS and intraventricular block are noted occasionally The electrocardiographic changes appear in the second week of the disease and disappear within a month or two but a prolongation of the QRS may persist[134]

Marked improvement in fever and clinical course of severe trichinosis with myocardial involvement has followed adrenocorticoid therapy[128 133]

ECHINOCOCCUS INFECTIONS

Cardiac involvement by echinococcus (hydatid) cysts occurs rarely and in about 0 5 to 1 per cent of all echinococcus disease Dévé[139]

analyzed 137 cases of cardiac echinococcus disease, in 83 per cent of which the primary echinococcus infestation was limited to the heart while in the remainder the cardiac cyst coexisted with one or more primary cysts in other organs, particularly the liver Any chamber of the heart may be involved with cysts, which vary in size from that of a cherry to that of an orange A review of echinococcus cyst of the left side of the heart was presented by Peters and associates [144]

In the absence of complications there are no symptoms, the cysts being found accidentally at postmortem examination Some patients suffer from palpitation, arrhythmias, attacks of dyspnea or precordial oppression Local effects of large cardiac cysts include peculiar murmurs , enlargement of the cardiac silhouette or bizarre shadows in the cardiac contours on roentgenologic examination Involvement of the interventricular septum has caused intermittent heart block with Adams Stokes syndrome [141] Pericarditis, polyserositis and constrictive pericarditis may occur, an instance of the latter having been cured by surgery

Single or recurrent rupture of a cyst into the cardiac cavity may cause (a) sudden death from anaphylactic shock or obstruction of a valvular orifice, (b) anaphylactoid reactions with anxiety vomiting and shock (c) embolism of cysts with obstruction of the vessels to the brain lungs abdominal viscera or extremities [145] Recovery may be complicated by hemiplegia gangrene or renal shutdown Rupture of the cysts into the pericardium occurs occasionally with inflammatory reaction and adherent pericardium

Diagnosis may be suggested by the combination of (a) echinococcus cyst elsewhere, blood eosinophilia and positive skin or serologic tests for echinococcus, together with (b) suggestive roentgen ray evidence of calcified cysts in the heart, bizarre shadows in the cardiac silhouette, peculiar cardiac murmurs or a sudden anaphylactic shock like syndrome with or without embolization Diagnosis is important because of the possibility of surgical treatment An echinococcus embolism of the axillary artery was removed by Kohler [142] In several cases cardiac echinococcus disease was diagnosed during life [139] In one case the diagnosis was made roentgenographically and treated successfully by operation [143]

TRYPANOSOMIASIS (CHAGAS' DISEASE)

This is a common South American disease caused by the Trypanosoma cruzi and transmitted by a bedbug vector, the Panstrongylus magistus [146] It occurs as an acute generalized disease in which the myocardium is almost always involved, and as a chronic disease with predominant cardiac manifestations [147] In the acute form there are diffuse myocardial lesions with extensive destruction of muscle fibers associated with a mononuclear interstitial myocarditis In the chronic form there is a predominant interstitial myocarditis with infiltration of lymphocytes plasma cells mononuclears and macrophages and diffuse fibrosis All parts of the heart are involved

The acute form of the disease is dominated by generalized evidences of toxemia and disseminated lesions, but sudden death may result from cardiac involvement The chronic form is characterized by insidious onset, profound weakness, palpitation and precordial pain, dyspnea on effort, cardiac enlargement and all the objective evidences of progressive congestive heart failure The clinical picture may simulate coronary artery disease [150] Syncope occurs commonly and may be due to complete heart block Sudden death occurs frequently A special characteristic of the disease is the frequency of all forms of arrhythmias and conduction disturbances [148, 151] These include marked bradycardia, partial and complete heart block premature contractions atrial flutter and fibrillation and right bundle branch block [149] The QRS complexes are of low voltage Rosenbaum and Alvarez[152] in Buenos Aires observed electrocardiographic abnormalities in 113 (86 9 per cent) of 130 cases of the chronic form of Chagas' disease Right bundle branch block occurred in 5 , per cent ventricular extrasystoles in 53 9 per cent, primary T wave changes in 42 4 per cent P wave abnormalities in 23 per cent and left ventricular enlargement in 22 1 per cent

CARDIAC DISEASE DUE TO OTHER INFECTIONS, INTOXICATIONS, DRUGS OR PHYSICAL AGENTS

Electrocardiographic or pathologic evidence of myocardial involvement has been described in a variety of other infection among them focal infections,[153] bronchiectasis and a number of bacterial infections besides those specifically discussed Pericarditis in

cluding constrictive pericarditis due to Pasteurella tularensis has been noted[169] (p 609) Electrocardiographic changes and evidence of myocardial pericardial and endocardial involvement have been reported in Reiter's disease [173, 171, 165] Myocarditis pericarditis or endocarditis has also been noted occasionally in infections with other higher bacteria yeasts or fungi such as coccidioidomycosis [167] blastomycosis torulosis toxoplasmosis [172] histoplasmosis[17, 174] and sarcosporidia [150] Schistosomiasis (bilharziasis) secondarily causes cor pulmonale by producing an extensive obliterating pulmonary endarteritis (p 982) Rarely an amebic pericarditis complicates an amebic abscess of the left side of the liver [156] Myocardial lesions are occasionally observed in malaria as a result of plugging of the coronary capillaries by erythrocytes involved by malarial parasites [170]

Myocardial lesions have been attributed to the metabolic toxins associated with uremia (p 994) and those associated with extensive burns [156] serum sickness [199] and cutaneous lesions [134] Myocardial infarction has been reported during or shortly after serum sickness a wasp sting administration of tetanus antitoxin penicillin and fever therapy [176] Considerable interest has been aroused by the finding of severe interstitial myocarditis following the experimental or clinical administration of sulfonamides [191, 180] A case of eosinophilic and giant cell granulomatous myocarditis associated with exfoliative dermatitis was attributed to penicillin hypersensitivity [179]

Phosphorus poisoning may produce intense fatty degeneration of the heart and electrocardiographic abnormalities [181] but the clinical picture is dominated by concomitant hepatic damage *Carbon monoxide poisoning* will be discussed (p 1093) Cardiac abnormalities due to overdosage with digitalis (p 265) and quinidine (p 370) have also been discussed Myocardial necrosis and calcification have been observed following poisoning with bichloride of *mercury* Acute interstitial myocarditis has been described in a case of exfoliative dermatitis following arsphenamine administration [177] *Emetine* causes inversion of the T waves in two or more leads occasional changes in the QRS complex dyspnea tachycardia apical systolic murmurs and even gallop rhythm [180, 170] De Cossio[18] described T wave inversions in the precordial leads in all patients and Q T prolongation in 90 per cent of those receiving emetine appearing usually one week after administration of the drug is begun The electrocardiogram may resemble or indicate that of myocardial infarction with respect to RS T elevations and T wave inversions [158a] [illegible] Fatal myocarditis due to emetine has been reported [156]

Deep ST depressions or T wave inversions were noted in electrocardiograms of patients receiving tetraethylthiuram disulfide (Antabuse) therapy for alcoholism at the height of an alcohol test reaction [183] This was interpreted to denote latent coronary insufficiency or myocardial anoxia and was occasionally associated with a fall in blood pressure and a shock like picture

Myocardial lesions have also been noted following deep roentgen ray therapy to organs adjacent to the heart [186]

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Chapter 37

THE HEART IN HYPERTENSION AND RENAL DISEASE

THE HEART IN HYPERTENSION

HYPERTENSION AND HYPERTENSIVE HEART DISEASE

Hypertensive heart disease is generally regarded as the commonest form of cardiac affection. Nevertheless the exact kinship between hypertension and heart disease is obscure and the delineation of hypertensive heart disease as a pure etiologic entity, independent of other forms of heart disease, is ill defined.

The causal relationship of hypertension to heart disease is based first of all on the frequency with which the two conditions are associated.[53] In a series of over 30 000 autopsies with 4700 cardiovascular deaths about 45 per cent of the latter were due to hypertensive heart disease.[33] The course of hypertension also supports its relationship to heart disease, for at least 60 to 75 per cent of hypertensive patients ultimately succumb from cardiac complications, especially heart failure.[11, 53, 149, 198] Finally it is believed that the physiologic disturbances associated with hypertension are such as to impose a serious strain on the heart (p 927). In summary the concept of a form of heart disease due to hypertension, per se, is based on (1) the very high incidence of hypertension in cases of heart disease, (2) the predominant frequency of ultimate cardiac disease in hypertensive patients, and (3) physiologic evidence that hypertension increases the work and otherwise strains or impairs cardiac function.

Hypertensive and Coronary (Atherosclerotic) Heart Disease

The exact causal relationship between hypertension and heart disease is obscured by two types of data.

(1) There is a lack of correlation in most cases between the severity and duration of hypertension and the development of cardiac complications.

(2) Hypertension is associated with a high incidence of coronary atherosclerosis. On the one hand Clawson,[3] in a necropsy study of about 1000 cases of coronary atherosclerotic heart disease, found that hypertension had been present in about 70 per cent. Conversely coronary sclerosis has been found in 90 per cent of hearts of persons dying with hypertension.[■] The relative importance of coronary atherosclerosis and hypertension in producing clinical heart disease is suggested by the clinicopathologic observations of Averbuck.[7] In two similar groups of hypertensive cases which came to autopsy, significant coronary atherosclerosis was found in 85 per cent of those with clinical heart disease and in only 10 per cent of those without heart disease.

Careful clinical and pathologic study of the problem over many years has impressed me with the predominant importance of coronary atherosclerosis in determining the manifestations of so-called hypertensive heart disease. This concept does not exclude any causal relationship between hypertension and the coronary atherosclerosis or the possibility of some common mechanism. Nor does it exclude the mechanical or other effects of hypertension on the heart which increase its susceptibility to injury by means of a deficient coronary blood supply.

Occasionally, and particularly in the experience of coroners, sudden death in hypertensive individuals is associated with pronounced cardiac hypertrophy and heart weight exceeding 400 gm, without significant coronary disease. In such cases the cardiac disease and sudden death are attributed exclusively to hypertension, in the absence of any other discoverable cause. In cases of malignant hypertension heart failure develops frequently in the last stages while coronary atherosclerosis is usually not severe. The heart failure may be

attributed to the strain of the hypertension and the consequent pronounced cardiac hypertrophy, but renal impairment in the excretion of sodium and water may also be an important causative factor

Systolic and Diastolic Hypertension

The clinical features and complications which characterize the disease hypertension or essential hypertension appear to be related to an elevated diastolic blood pressure rather than an elevated systolic blood pressure As a rule the systolic blood pressure *also is elevated when there is diastolic hypertension* but systolic hypertension may occur without elevation of the diastolic pressure In older individuals especially beyond the age of 60 the systolic pressure and the pulse pressure quite commonly increase although the diastolic pressure remains relatively unaltered It is believed that this rise in systolic pressure is related to atherosclerosis of the aorta and diminished elasticity of this large vessel Although a rise in the systolic pressure is usually associated with an increase in mean pressure and therefore in the work of the heart alone it appears to be of little significance in the development of clinical heart disease or of renal or cerebral impairment

NORMAL BLOOD PRESSURE AND HIGH BLOOD PRESSURE (HYPERTENSION)

There is no universal agreement as to the dividing line between normal and high blood pressure On the basis of various measurements of blood pressure in normal individuals follow up studies of military personnel and mortality data of life insurance companies I have always regarded a persistent elevation of the diastolic blood pressure above 90 mm Hg as representing diastolic hypertension However in individuals past the age of 50 diastolic blood pressures up to 95 or even 100 mm Hg were considered as probably normal Corresponding to these diastolic pressures a systolic pressure of 150 mm Hg or above was regarded as representing systolic hypertension in individuals below the age of 50 Beyond that age systolic pressure of 160 to 170 mm Hg were commonly regarded as normal More recently studies by Master and his associates[1,4] Hamilton Pickering and associates[80] and others have indicated that there is a progressive rise of diastolic as well as systolic pressure with age and that the range of normal blood pressure[7] is higher than the figures just stated Actually the blood pressures found by these observers represent the *frequency distribution of* blood pressure levels among men and women at various ages obtained under the particular conditions of their observations[179] Whether the blood pressures of the majority of individuals of a given sex and in a given age range thus obtained represent *normal* blood pressures remains to be determined

The determination of the arterial blood pressure and the evaluation of normal blood *pressure versus hypertension are* beset by at least three difficulties

1 The Accuracy of the Determined Blood Pressure

This need not be a significant problem for the indirect method of blood pressure determination using auscultation and the sphygmomanometer is quite satisfactory and accurate when performed with care There is reasonable agreement between direct intra arterial measurements and those obtained by the indirect method[81,316] The indirect readings average about 4 mm lower than the direct for the systolic pressure and 9 mm higher for the diastolic pressure The closest correlation between the two methods with respect to diastolic pressure is said to be obtained when the cessation of sounds rather than the sudden diminution in intensity is taken as the criterion[81] but this view has been disputed by Roberts and associates[184] Error may be introduced in the measurements of the blood pressure of obese individuals with large arms When the standard cuff width of about 13 cm is used the auscultatory blood pressure tends to be too high in persons with obese arms and too low in those with thin arms[179]

2 Casual and Basal Blood Pressures

Significant variations in blood pressure may occur at different times of the day and from day to day owing to emotional and other factors unrelated to organic disease Pressures determined without regard to the time of day or environmental factors and without special preparation of the patient are termed *casual blood pressures* If several such readings are taken repeatedly after brief intervals of a few minutes there may be variations of slight or considerable degree When variations are large the blood pressure is termed labile blood pressure If hypertensive levels are reached in some of the measurements the subject is said to have *labile hypertension* Some physicians

make repeated determinations of casual blood pressures at intervals of several minutes and use the lowest blood pressure. Others may make a single casual determination. Blood pressures determined as soon as the patient awakens and before he gets out of bed are usually lower than at any other time in the day and are termed *basal blood pressures*. These are less variable than casual blood pressure determinations. In hypertensive patients particularly, both the casual and the basal blood pressure readings may fall to a variable extent after a period of a week or more of complete bed rest.

3 Criteria of Normal Blood Pressure Versus Hypertension

It is difficult to compare the data of different investigators as a basis for setting up criteria for normal and elevated blood pressure. There may be a significant error in statistical data based on blood pressures determined casually with varied techniques by a host of different observers who are unaware that such isolated measurements will be used for determining "normal" standards. In addition the material used is not comparable. In some studies the samples tended to exclude subjects with blood pressures above an arbitrary level, for example, applicants for certain types of standard insurance. Other samples were so chosen that subjects with definitely abnormal blood pressures may have been included. The stated upper limits of normal blood pressure have varied from approximately 140 mm Hg systolic and 90 mm Hg diastolic[18, 185] to 200 systolic and 110 mm Hg diastolic,[3, 14, 35] the latter pressures in older subjects.

Assuming that there is a progressive rise in blood pressure with age and that more than 35 per cent of individuals between the ages of 60 and 64 have a diastolic blood pressure above 100 mm Hg may this not signify that more than 35 per cent of individuals in this age range in this country and in Great Britain suffer from at least mild or moderate hypertension rather than that they are experiencing a normal increase in blood pressure due to the aging process? Attention is called to a possible analogy to the increased incidence of hypercholesterolemia and coronary heart disease with aging in the same countries, and the question whether this denotes normalcy or a pathologic process. It will be of interest to discover whether the described rise in blood pressure with age occurs in countries in which hypertension is a less common disease.

The distinction between hypertension and normal blood pressure possesses significance insofar as the former is associated with a higher incidence of clinical symptoms and complicating disease and with a diminished life expectancy. A given blood pressure range may not be regarded as normal for a given age or sex, regardless of its frequency, if it is associated with a higher incidence of illness and mortality than lower blood pressure levels in the same age group. There is suggestive evidence that in any age group the incidence of cardiac, renal and cerebral complications and the mortality rate are higher when the diastolic pressure exceeds 90 mm Hg and the systolic is simultaneously above 140 mm Hg than when the blood pressures are below these levels.[185, 49] Army officers with even moderate degrees of transient hypertension developed sustained hypertension more frequently than those who had never had an elevated blood pressure, and showed a higher rate of retirement for disability and a higher death rate from cardiovascular renal disease.[120] There is greater need for studies correlating various ranges of blood pressure with the subsequent development of these complications and with life expectancy than for studies of the mere incidence of various blood pressure at different age levels. Too much stress should not be laid on the practical importance of an exact dividing line between normal and elevated blood pressure. Slight degrees of hypertension may actually have little more than statistical significance with respect to mortality and vascular complications. For the most part these complications and a shortened life expectancy are observed in individuals whose diastolic pressure exceeds 110 and especially 120 or 130 mm Hg. There is general agreement that pressures above these levels represent hypertension. The borderline levels of diastolic blood pressure concerning which there is disagreement may be important only insofar as they may be harbingers of still higher and more significant levels of blood pressure in later life.

ETIOLOGY OF HYPERTENSIVE HEART DISEASE

The etiology of hypertensive heart disease is obscured by uncertainty as to the genesis of the underlying hypertension. A detailed dis

cussion of hypertension, per se, is beyond the scope of this book. Only a brief résumé is given in order to obtain a better orientation towards its relationship to hypertensive heart disease.

Essential Hypertension and Secondary Hypertension

Hypertension is associated with or due to a variety of conditions, notably

(1) Renal diseases (acute and chronic glomerulonephritis, chronic pyelonephritis, polycystic kidneys, renal tumors, periarteritis nodosa, renal vascular anomalies and occlusions, toxic nephroses),

(2) Endocrine diseases (Cushing's syndrome, pheochromocytoma),

(3) Vascular disease (coarctation of the aorta, acute porphyria),

(4) Cerebral lesions (brain tumor, bulbar poliomyelitis).

Hypertension associated with these primary diseases is sometimes termed secondary hypertension. In the largest group of hypertensive cases no apparent underlying disease can be discovered. These are therefore termed "primary" or essential hypertension.

THEORIES OF HYPERTENSION

The pathogenesis of hypertension in the large group of cases termed essential hypertension is unknown. Such observations as appear pertinent have related the hypertension to disturbances of (1) the endocrine organs, (2) the kidney or (3) the central nervous system. In addition, humoral pressor agents generated by metabolic or other disturbances have been considered as possible etiologic factors. It has also been postulated that the arterioles may become abnormally sensitive to normally circulating pressor agents. Finally, it is possible that there are different kinds of hypertension within the category known as essential, and that more than one of the above factors may be concerned in individual cases of hypertension.

Endocrine Theory

Tumors of the adrenal medulla (p. 1025) cause paroxysmal or persistent hypertension but they do not account for the vast majority of cases of this essential hypertension. Nevertheless Palmer[151] still believes that norepinephrine may be responsible for essential hypertension. More significant is the hypertension associated with hyperfunction of the adrenal cortex as exemplified by Cushing's syndrome (p. 1024). Toxemia of pregnancy with its associated hypertension may be related to adrenal cortical steroids which are found in the placenta. Conversely, there is pronounced hypotension in Addison's disease in which there is a deficiency of the adrenal cortex. In cases of Addison's disease the continued administration of the synthetic adrenal cortical hormone desoxycorticosterone (DCA) together with sodium chloride may produce hypertension[166] (p. 1024). The same procedure in hypertensive patients leads to further elevation of the blood pressure.[159, 164] DCA has also been found to have an immediate pressor effect when injected intravenously in hypertensive individuals.[74] In animals, the adrenals appear to be necessary to the production or maintenance of experimental hypertension by renal ischemia,[145] and DCA has been reported to produce hypertension and atherosclerosis in rats.[199] Selye[201] has postulated that hypertensive vascular disease, as well as other diseases, results from adrenocortical secretion in response to various non-specific "stresses" (alarm reaction). Genest et al.[68] suggested that hypertension could result from a state of mild and chronic hyperaldosteronism. But although as a rule the adrenals are necessary for hypertension, animals have been made hypertensive even after adrenalectomy.[116] Even more significantly, marked hypertension has persisted in some patients even after bilateral adrenalectomy.

These observations may indicate merely that the endocrine glands are responsible for one small group of cases of hypertension, or that the adrenal cortex in particular may be one element in a complex cycle of events leading to human hypertension. Concepts attributing to the adrenal cortex and/or to the pituitary hypothalamic centers a major role in hypertension have been formulated by Selye[90] and by Heinbecker.[95]

Sodium and Hypertension. The sodium ion is in some way related to the development of certain forms of experimental hypertension[9, 77] and possibly also human hypertension.[164] However, the sodium ion is not directly responsible for hypertension. The relationship of sodium to hypertension was most strikingly indicated by the beneficial effect of a very low sodium diet in the treatment of many patients with essential hypertension (p. 935). There is some evidence that there is a low incidence of hypertension in races with a low sodium intake

in their diet No hypertension was observed in any individuals of a group of adults whose spontaneous sodium intake was low This suggested a hypothesis that a minimal level of sodium intake must be exceeded for the development of hypertension although the sodium in itself is not sufficient for its development [39] Hypertensive individuals behave differently from normals in their response to rigorous sodium restriction[18] and to acute salt loads [5] Hypertension has been produced in the rat by substituting hypertonic chloride solutions for drinking water,[188] and a high correlation has been found between an elevation in blood pressure and the concentration of sodium chloride fed to male albino rats [132]

Restriction of dietary potassium in hypertensive patients also has been noted to result in small but significant decreases in blood pressure despite sodium retention [26]

Renal Genesis of Hypertension

1 Association with Intrinsic Primary Renal Disease The association of hypertension with a variety of intrinsic diseases of the kidney has long been known In these cases the bilateral renal disease precedes the hypertension and is generally regarded as the cause of the hypertension but the mechanism is uncertain

2 Experimental Production of Hypertension by Renal Ischemia However, a renal origin for essential hypertension as well was given renewed impetus when Goldblatt and his associates[73] induced pronounced and persistent hypertension without renal excretory insufficiency in dogs by bilateral constriction of the renal arteries Subsequently renal hypertension was induced by Page[146] by investing the kidney with cellophane which formed a fibrocollagenous compressing hull The experiments of Goldblatt and his associates led to the concept that human essential hypertension, like the experimental form might be the result of renal ischemia But, except for occasional instances of hypertension the Goldblatt mechanism is no longer regarded as a basic factor in the pathogenesis of essential hypertension

3 Unilateral Renal Arterial and Urologic Disease Further support of the concept of a renal genesis of hypertension is found in the striking instances of hypertension following unilateral renal arterial occlusion e g by embolism,[53] thrombosis,[76] atheromatous plaque[10] or external compression,[104] in cures of such cases of hypertension by unilateral nephrectomy, and in cases of unilateral urologic disease and hypertension in which the hypertension was cured by removal of the diseased kidney [20 87 176 101]

4 Renal Pressor Substances Finally, the demonstration of pressor substances related to the ischemic kidney in the experimental animal, and the purported similarity of the hypertension induced by such pressor substance to experimental renal hypertension have also been advanced as evidence for the renal genesis of hypertension[147] (v infra) There is also evidence that the normal and not the ischemic kidney excretes something which may be responsible for hypertension [?] Grollman and associates[85] showed that hypertension may occur in the absence of both kidneys, provided excretion is effected by peritoneal lavage Their observations and those of Handler and Bernheim[8] suggest that the kidney normally produces a substance which prevents the occurrence of hypertension Hypertension may follow absence or diminution of this renal antipressor substance The possibility has also been considered that hypertension occurs when a normal pressor substance produced in the kidney or elsewhere is abnormally retained because of renal dysfunction [?] But there is usually no renal impairment in essential hypertension, except in very advanced stages of the disease

5 Renal Arteriolosclerosis in Essential Hypertension Renal arteriolosclerosis is almost universally present in autopsied cases of essential hypertension [15 57] Whereas Fishberg[57] interpreted these findings as secondary to hypertension Moritz and Oldt[134] concluded that they were evidence of a primary diminution in renal blood flow and therefore supported the renal pathogenesis of essential hypertension In a series of 500 renal biopsies taken in the course of sympathectomy for hypertension Castleman and Smithwick[30] found that there was no vascular disease or only insignificant lesions in about 25 per cent and Heptinstall[?] in a similar study found only slight vascular changes in approximately 60 per cent of 50 renal biopsies They concluded that hypertension therefore preceded the development of renal arteriolosclerosis Goldblatt[7] has objected that the small specimens taken do not necessarily reflect the vascular status of the entire kidney

A more detailed discussion of the arguments favoring the renal mechanism of hypertension may be found in Goldblatt's[72] review and of

the opposing viewpoint in a review by Smith, Goldring and Chasis [96] Despite uncertainties as to the exact mechanism relating the kidney and hypertension, *the weight of evidence strongly suggests that the kidney may be an important link in the pathogenesis of hypertension*

Neurogenic and Humoral Factors in Hypertension

Since it has been long known that sympathetic vasoconstriction of the splanchnic vessels can elevate the blood pressure conspicuously it was thought that the arteriolar constriction of human hypertension was due to this neurogenic mechanism This viewpoint has been supported by the observation that a substantial fall in blood pressure follows sympathectomy in humans with hypertension In man increased intracranial pressure is associated with elevation of blood pressure and hypertension may occur in bulbar poliomyelitis and other diseases of the brain Psychic factors have been related to hypertension by their effect on the central nervous system as well as by stimulating the secretion of norepinephrine

On the other hand there are many studies which seem to cast doubt on or minimize the importance of the sympathetic nervous system in the pathogenesis of essential hypertension The fall in blood pressure following sympathectomy in clinical hypertension is often absent or insignificant or transient Despite extensive sympathectomy the blood pressure is rarely restored to normal A moderate fall in pressure after sympathectomy might denote merely the elimination of the normal vasoconstrictor element of the blood pressure without modification of the abnormal and excessive arteriolar tonus responsible for the hypertension There is as yet insufficient evidence that the central or sympathetic nervous system plays a primary role in the production of essential hypertension

In experimental renal hypertension a neurogenic factor has been excluded because (1) total sympathectomy does not prevent or abolish the hypertension induced by constriction of the renal artery [4] (2) transplantation of an ischemic denervated kidney to the neck of a different bilaterally nephrectomized dog induces hypertension [4] or hypertension may be induced by constriction of the renal artery after the kidney has been transplanted These experiments indicate that a humoral agent is responsible for the hypertension

More direct support for a humoral mechanism of hypertension is provided by the finding of a number of substances which are believed to account for experimental renal hypertension [8 8] The following schema has been evolved [147 7 43]

1 Renin [7] is an enzymatic substance formed in normal and hypertensive kidneys which enters the blood stream through the renal vein and acts upon

2 Hypertensinogen (renin activator), an alpha globulin produced in the liver and found in the plasma to produce

3 Hypertensin[139] (angiotonin[140]), a polypeptide which is a powerful pressor and vasoconstrictor This can be inactivated by

4 Hypertensinase, an enzyme produced, among other organs by normal kidneys and found in the blood

Other pressor substances obtained from kidney have been suggested as possible agents in the mechanism of hypertension, including the vasoexcitor material (VEM) of Shorr et al [20] (p 303) and pressor amines reported to result from defective deamination of amino acids in the anoxic kidney [16] Schroeder and Olsen[137] discovered an amine like pressor substance in the blood of patients with hypertension which they termed *pherentasin* It is uncommon in the blood of normotensive subjects A host of other pressor substances have been described but there is no consistent association with hypertension None is invariably present in the blood of hypertensive patients, and they are found in some normal individuals An antibody to renin (antirenin), capable of neutralizing the pressor effect of an intravenous injection of renin, has been described [229] A possible relation of hepatic metabolism or hepatic detoxification of sex hormones is suggested by the finding of a remarkably low frequency of hypertension and cardiac hypertrophy at autopsy in women who were found to have subchronic hepatitis at autopsy [278]

A causal relationship between these humoral agents and experimental renal hypertension is probable, their significance for human hypertension is hypothetical

OTHER ETIOLOGIC FACTORS

Age

Hypertension is uncommon before the age of 20 Thereafter it is encountered in 20 to 25 per cent of the general population and in

to 60 per cent of those beyond the age of 50[125] Hypertension before the age of 20 occurs chiefly with coarctation of the aorta, acute or chronic glomerulonephritis and rarely with endocrine tumors or unilateral renal disease

Sex

Hypertension is slightly more common in the female but hypertensive (and atherosclerotic) heart disease is much more frequent in the male Data on these points are not in agreement

Race and Environment

An increased incidence of hypertension is often related to the accelerated tempo of modern industrialized civilizations Perhaps the purported increase in hypertension in western civilization is due to dietary differences which disturb metabolism, rather than to increased environmental stress Negroes in Africa rarely suffer from hypertension,[44] but in the United States hypertension is more frequent and more severe in Negroes than in whites [11] Similar observations have been made with respect to Chinese who emigrate to the United States Cohen[35] concluded that hypertension was rare in the Indians in the southwestern portion of the United States There were only 14 instances of hypertension among 1140 admissions There are many pitfalls in attempting to draw conclusions of reported differences in incidence of hypertension among various regional and racial groups [11]

Heredity

There is suggestive evidence of a familial tendency to hypertension [175, 80, 185, 176] This evidence consists of records of hypertension in *many members of a family of the occurrence* of hypertension in twins[211] and the tendency to higher pressures in relatives of patients with hypertension as compared with relatives of individuals with normal blood pressures [211, 80] Thomas[27] found that among medical students with at least one parent who had hypertension or coronary heart disease there was a significant number with a high resting blood pressure and heart rate and with hyperreactivity to the cold pressor test Hypertension was found to be three times as frequent among siblings of hypertensive individuals as among siblings of normotensives [224] Hypertension is said to be inherited as a dominant characteristic [11, 211] Statistical evaluation of small series of cases is difficult because of the frequency of hypertension in the general population, or because of disagreement as to standards of normal and elevated blood pressure

Constitution

Hypertension has been related to body build and constitution [185] It is commoner in the obese, and occurs with some predilection for the short, low necked, stocky individual There are certainly many exceptions The hypertensive individual is characterized as a hyperreactor with exaggerated response to cold, epinephrine, etc

Temperament and Emotion

Psychologic disturbances have been postulated as initiating factors in hypertension Transient, and occasionally permanent hypertension has been found to follow repeated powerful emotional experiences involving fear, anxiety and hostility, e g , in the course of battle Palmer[181] regards hypertension as a "chronic emergency response in congenitally susceptible individuals due to the strain of adjustment to the environment " A characteristic hypertensive personality[18] and distinctive psychiatric pattern[8, 17] have been described [181] Subnormal assertiveness, dependence, suppressed hostility and obsessive-compulsive traits are commonly noted in hypertensive patients,[79] but similar traits have been described in other organic diseases supposedly due to psychic factors Undoubtedly many of the *symptoms* associated with essential hypertension are of psychic origin However, there is little scientific evidence to indicate that psychic disturbances are the prime cause of *hypertension* Experiments indicating that the blood pressure rises or the renal plasma flow diminishes when certain *emotional stresses* are introduced into the conversation or experimental situation[51, 60] do not have direct bearing on the problem of the pathogenesis of hypertension

PATHOLOGIC PHYSIOLOGY

Circulatory Dynamics

The *cardiac output* is normal in uncomplicated hypertension [22] Since the blood pressure is elevated, the *peripheral arterial resistance* must be *increased* to approximately the same degree [11] The viscosity of the blood is altered insignificantly

The increased peripheral resistance, due to widespread constriction of the arterioles and minute arteries, is the fundamental vascular alteration in essential hypertension The arterial pressure rises because the volume flow

of blood (cardiac output) in the arterial tree is unchanged while the capacity of the arterial tree is reduced by vasoconstriction

The cause of the increased peripheral resistance and the responsible mechanism are unknown The responses to sympathectomy hypotensive drugs and greatly restricted sodium intake suggest that various mechanisms may be causative in different hypertensive individuals Arteriolar constriction responsible for the increased peripheral resistance is due primarily and chiefly to increased tone but intrinsic structural changes (widespread intimal thickening and medial hypertrophy) may contribute to the arteriolar narrowing

That the heart is capable of maintaining its normal output despite the increased resistance to outflow is due to compensatory cardiac dilatation and hypertrophy (p 91) If humoral substances are concerned in the pathogenesis of hypertension these substances may aid in maintaining the normal cardiac output against increased peripheral resistance by increasing myocardial efficiency

The *work of the heart in hypertension* can be calculated though imperfectly by multiplying the cardiac output and the mean arterial pressure[193] The kinetic energy of ejection is ordinarily a negligible factor but it may be more important in hypertension because of the increased velocity of ejection of blood[38] Since the cardiac output is normal the work of the heart is increased approximately in proportion to the elevation of arterial pressure

The *circulation time* is normal in the absence of heart failure

The *venous pressure* is normal as is the right atrial pressure measured directly by intracardiac catheterization

The *circulating blood volume* is normal in the absence of heart failure

Mechanism of Cardiac Disease and Cardiac Failure in Hypertension

Cardiac disease and failure in hypertension may be due to

(1) Increased work of the heart leading to cardiac dilatation and hypertrophy The blood supply does not keep pace with the increase in muscle mass and there is relative anoxia This disparity is exaggerated with the development of coronary atherosclerosis

(2) Hypertension accelerates and intensifies the development of coronary atherosclerosis (p 429) The development of cardiac failure may be due predominantly to coronary insufficiency

(3) With advancing hypertension impairment of renal blood flow and renal excretory function become significant factors A deficiency in the renal excretion of sodium and water would intensify any tendency to congestive heart failure

PATHOLOGY

The essential cardiac abnormality is hypertrophy of the left ventricle[100] In patients who succumb from non-cardiac causes dilatation is minimal (so-called concentric hypertrophy) This is probably due to the gradual evolution of the hypertension which permits effective hypertrophy to develop without apparent dilatation The hypertrophy involves first the outflow tract (p 102) or anterior half of the left ventricle and later also the inflow tract

In cases of hypertension with heart failure dilatation and hypertrophy may both be pronounced Although the left ventricle is predominantly affected the right chambers may also be dilated and hypertrophied Studies of heart weights of individual cardiac chambers in hypertension indicate that the right ventricle hypertrophies only with the advent of heart failure[101]

Coronary atherosclerosis with or without severe narrowing and with or without occlusion and infarction is commonly present Many of the pathologic findings in so-called hypertensive heart disease are due to atherosclerosis of the coronary arteries (p 429) Ischemic necrosis occurs in malignant hypertension

CLINICAL FEATURES AND COURSE

Hypertension imposes a load on the heart which for many years may be compensated by left ventricular hypertrophy Eventually in more than half the cases this compensatory mechanism is inadequate and congestive heart failure appears Accordingly hypertensive heart disease is often classified into two categories (1) the compensated stage and (2) the decompensated stage

Compensated Stage of Hypertensive Heart Disease

There are no symptoms referable to the heart unless there is advanced coronary atherosclerosis Angina pectoris or an acute attack of coronary occlusion and myocardial infarction may occur There may be symptoms

on the clinical picture which is described on page 1024

Classification of Hypertension According to Severity

One of the most widely used sets of criteria of the severity of hypertension is that of Keith Wagener and associates [111] who classified a series of 219 cases according to the severity of the changes in the optic fundus as follows

Grade I Mild narrowing or sclerosis of the retinal arteries The arteries are narrowed relative to the caliber of the veins Normally the arteriovenous diameter ratio is about 4 to 5

Grade II Moderate to marked sclerosis with exaggerated light reflex and compression of veins at arteriovenous crossings

Grade III Angiospastic retinitis, with edema cotton wool exudates and hemorrhages in the retina superimposed on sclerotic and spastic arteries The ratio of the diameter of artery to vein is progressively decreased At some points arterioles have disappeared and may not reach the periphery of the retina

Grade IV Papilledema or choking of the disk (edema and elevation) in addition to the vascular exudative and hemorrhagic lesions described in Grade III

These grades of increasing severity of retinal lesions correspond in a general way to progressively higher diastolic pressures and increased incidence of symptoms and complications

Based on another extensive series of cases Smithwick[209] devised a more complex system of classification, giving a numerical value to various unfavorable factors These factors were graded I to IV according to severity The following groupings were listed

Grade I Fundus Grade I according to the above Keith Wagener classification No cardiac, renal or cerebral complications

Grade II Fundus Grades II, III (or IV), but no cerebral cardiac or renal complications If any of these complication are present, the patient is still classified as grade II if the fundus shows only zero or Grade I lesions

Grade III Diastolic pressure below 140 with cerebral, cardiac or renal complications, but not the severe complications listed under Grade IV Fundus Grades II or III (or IV)

Grade IV Resting diastolic blood pressure 140 mm Hg or more If the diastolic pressure is below 140, then the hypertension is still classified Grade IV if there is a history of a cerebrovascular accident with a residual or there is frank congestive heart failure or the phenolsulfonphthalein test shows less than 15 per cent excretion in 15 minutes Usually Grades III or IV fundus

Other classifications of hypertension according to severity have been evolved Many of these distinguish (I) mild (II) moderate (III) severe hypertension, and (IV) malignant or accelerated phase of hypertension *(I) Mild hypertension* is characterized by systolic blood pressures below 200 and diastolic blood pressures below 110 mm Hg or by intermittent elevation in blood pressure (labile hypertension) *(II) Moderate hypertension* is characterized by systolic pressures of 200 to 230 and diastolic pressures of 110 to 120 mm Hg Symptoms may or may not be present There is good renal function *(III) Severe hypertension* is characterized by systolic blood pressures between 230 and 280 and diastolic blood pressures between 120 and 140 mm Hg which are relatively fixed As a rule, in these cases there are both symptoms and evidences of complications with respect to the cardiac renal or cerebral vascular systems *(IV) Malignant hypertension* has been defined by its accelerated progression and various clinical manifestations but the essential criterion is the presence of papilledema of the fundus in addition to exudates, hemorrhages and vascular narrowing As a rule the diastolic blood pressure is 130 mm Hg or more The neuroretinal edema, including papilledema, has been related to the intense degree of elevation of the diastolic pressure with consequent elevation of intracranial pressure[183] and pathologic spasm with focal edema [29] Furthermore, reversal of malignant to benign hypertension is usually produced by measures which lower the diastolic pressure below a critical level [171] However, very high diastolic blood pressures may occur without neuroretinitis (papilledema) [221] Conversely, neuroretinitis has been noted after the disappearance of hypertension [160] There is usually a brief stage in which malignant hypertension is associated with little or no renal impairment There is a later stage of compensated renal insufficiency and finally, before long a stage with azotemia or uremia Cardiac failure is common in malignant hypertension

Investigation of the hypertensive patient should include not only a complete history and physical examination blood pressure measurements and examination of the fundus but also roentgenologic examination of the chest for the size and configuration of the heart an electrocardiogram and such additional tests as may be necessary to determine cardiac function including the presence or absence of heart failure It is also important to establish the presence or absence of underlying renal disease and especially the state of renal function by examination of the urine a concentration test the 15 minute phenolsulfonphthalein excretion test and the determination of blood urea nitrogen or non protein nitrogen

DIAGNOSIS OF HYPERTENSIVE *HEART DISEASE*

The diagnosis of hypertensive heart disease in the compensated stage is based on the combination of persistent diastolic hypertension and evidence of left ventricular hypertrophy (roentgenologic and electrocardiographic)

The combination of diastolic hypertension and left ventricular hypertrophy together with evidence of (a) angina pectoris (b) coronary occlusion and myocardial infarction (c) congestive heart failure and/or (d) electrocardiographic signs of intraventricular conduction disturbances should justify a diagnosis of hypertensive and coronary (atherosclerotic) heart disease if aortic stenosis is excluded

PROGNOSIS

Variable Outlook According to Different Observers

The prognosis in untreated hypertension has assumed increasing importance as new measures have been introduced for its treatment Keith Wagener and Barker[111] reported on the mortality rates for various groups of hypertensive patients based on their classification according to changes in the optic fundus after a follow up period of five to ten years The mortality rates were 40 per cent in Grade I 65 per cent in Grade II 92 per cent in Grade III and 99 4 per cent in Grade IV after the above interval Using the same criteria for classification Palmer and his associates[1] reported mortality rates in 430 cases of essential hypertension after eight years to be 22 per cent in Grade I 47 per cent in Grade II 78 per cent in Grade III and 94 per cent in Grade IV Except for Grade IV the outlook was somewhat better than that reported by Keith et al[111] Many of the reports evaluating new therapeutic measures for hypertension compare results obtained with the control mortality rates reported by Keith and his associates Such comparisons are unduly favorable to the therapeutic agent because continued studies of the natural life history of hypertension indicate that the outlook is better than that reported by Keith and his associates except possibly in Grade IV representing the malignant or accelerated phase of hypertension

There is still need for further study of the natural life history of essential hypertension because of the tremendous variation in severity and course of different cases of clinical *hypertension and because of the wide range of* mortality rates reported by various observers who have followed large series of unoperated patients For example Perera[1 8] reported a 17 per cent mortality in a 12 year average follow up period of 250 cases Bechgaard[13] a 28 per cent mortality in a 4 to 11 year follow up of 1038 cases Hammarstrom and Bechgaard[55] a 51 per cent mortality in a 2 to 10 year follow up of 435 cases Palmer et al[14] a 61 per cent mortality in an 8 year average follow up of 430 cases whereas Keith Wagener and Barker[111] reported a still higher mortality in the 5 to 9 year follow up of their 219 cases Undoubtedly these variations in mortality rate are evidences of differences in type and severity of the cases of hypertension in the various series reported

It is becoming increasingly apparent that the life history of uncomplicated hypertension is usually very long[146 161 132 37] Perera[161] followed a group of 100 patients from the onset of their hypertension to death and found the average duration was 19 years when the onset occurred at an average age of 32 years The range of duration was between 3 and 34 years The average duration of life was 7 years after the onset of angina pectoris 5 years after the onset of albuminuria myocardial infarction or congestive heart failure 3 years after the onset of a cerebral vascular accident and 1 year after the onset of azotemia In 40 patients in whom the cause of death was determined death was due to congestive heart failure without myocardial infarction in 19 to myocardial infarction in 7 to a cerebral vascular accident in 17 and to uremia in 6 It should be empha

sized that even these results may not give as optimistic a picture as is warranted first because these data were based on patients who had already succumbed, whereas others followed in the same series may still be living, secondly, because hypertensive patients with the most favorable course and without symptoms or complications are not likely to come to the clinic or to specialists in hypertension

Outlook and Complications in Malignant Hypertension

The group classified as accelerated or malignant hypertension is a particularly important one because the criteria can be well defined and because the prognosis in this group is fairly well established Therefore the effectiveness of a given form of therapy can be best assessed in this group of cases Schottstaedt and Sokolow[191] in a study of 104 cases of malignant hypertension found survival time after discovery of the papilledema to be 13 months in patients with good kidney function at the time of diagnosis In 10 of these cases renal impairment developed in an average of 4 4 months In 91 patients with malignant hypertension, treated only symptomatically, uremia was especially frequent and only 3 survived for 30 months Smith and associates[207] in 376 cases of essential hypertension which were investigated at postmortem examination, found on the basis of the Keith Wagener criteria that uremia was the cause of death in only 3 per cent of Grade I in 2 per cent of Grade II in 15 6 per cent of Grade III and in 59 per cent of Grade IV which represents malignant hypertension In addition, congestive heart failure almost always complicates malignant hypertension before the end of its course The relatively rapid course and unfavorable outcome in malignant hypertension and the early and frequent development of uremia in malignant hypertension are elements which enable the use of this group of cases as a control for the evaluation of therapeutic measures

Height of Blood Pressure and Prognosis

The height of the blood pressure in general is correlated with the expectation of life according to insurance statistics Thus May[127] reported that in policy holders with blood pressures below 140 mm Hg the ratio of actual to expected mortality was 103 per cent, between 140 and 170 mm Hg the ratio was 134 per cent, in those with systolic pressures over 170 mm 220 per cent and in those over 200 mm 828 per cent The height of the diastolic blood pressure had an important influence on the mortality rate in the series of 151 hypertensive patients followed by Leishman[114] On the other hand recent studies are less definite regarding the question of prognosis and the height of blood pressure in hypertension But it appears that there is a significant rise in complications and mortality when the diastolic blood pressure exceeds 130 mm Hg and especially when it exceeds 140 mm Hg There are, however, occasional instances in which blood pressures of this range or higher are well tolerated for many years, particularly in women When, as is usually the case diastolic blood pressures of 140 mm Hg or higher are associated with the papilledema of malignant hypertension, the outlook is very unfavorable[20]

Prognosis of Hypertensive Heart Disease and Complicating Coronary Atherosclerosis

About 60 to 75 per cent of patients with hypertension succumb from cardiac complications, about 15 to 20 per cent from cerebral thrombosis, 5 to 10 per cent from uremia, and the remainder from dissecting aneurysm of the aorta or intercurrent diseases such as carcinoma, pulmonary embolism or infection[11, 44] When the heart is involved in hypertension the outlook is often determined by complicating coronary atherosclerosis, myocardial infarction and heart failure The development of congestive heart failure is a serious complication of hypertension, but the outlook is much better since the institution of strict dietary sodium restriction and the widespread use of mercurials Furthermore, heart failure often regresses following treatment of hypertension by diet, sympathectomy or hypotensive drugs The patient with hypertensive heart disease who was reported by Strade[216] to have lived for 32 years after the first incident of heart failure is an example of the most favorable possibility with good treatment The outlook becomes quite unfavorable when hypertension with heart failure is complicated by renal insufficiency This combination is observed notably in two circumstances (1) Malignant hypertension is complicated by congestive heart failure in a very high percentage of cases (2) Late in the history of treatment of congestive heart failure there is often an in

sidious or rapid development of renal insufficiency Whether this merely represents a terminal or terminating incident in the course of hypertensive heart disease with failure or whether it is the result of treatment of the heart failure per se is uncertain

Effect of Treatment on Prognosis[186a]

The most impressive evidence of the promising effectiveness of newer methods of treatment is the improved outlook in cases of so-called malignant or accelerated hypertension The amelioration or disappearance of the retinal abnormalities especially the papilledema the cardinal feature of malignant hypertension is a commonplace observation after treatment with very low sodium diet sympathectomy or the newer hypotensive drugs (p 936) Schottstaedt and Sokolow[191] pointed out that the disappearance of the papilledema in these cases indicates a decrease in the tempo of malignant hypertension and a reversal to benign hypertension However they stressed that vigorous treatment must be instituted in cases of malignant hypertension *before* renal function is impaired and before irreparable cardiac or cerebral complications have developed Smithwick[209] reported a mortality rate of 56 per cent among patients with malignant hypertension who underwent sympathectomy compared with a control figure of 100 per cent in the follow up period of 5 to 9 years Schroeder[195] reported that there was only a 9 per cent mortality in a period of 13 to 34 months among 212 patients with severe and malignant hypertension under treatment with hypotensive drugs On the other hand the mortality rate was 60 9 per cent in patients discontinuing treatment Among 106 patients with malignant hypertension studied during a three year period 28 discontinued treatment and 25 of these died within a month all of hypertension and its complications [196] The course of 10 with uremia was unaffected Of the 68 who continued treatment 14 died (21%) but only 3 as a result of complications of hypertension Thus 79 per cent of those who continued treatment were alive at least 15 to 36 months and most of these returned to full activity [196] The figure of 9 per cent mortality in 13 to 34 months may be compared with the figures of Schottstaedt and Sokolow[191] indicating that two thirds of patients with malignant hypertension die within 9 months

TREATMENT

CARDIAC MANIFESTATIONS

The treatment of heart failure of angina pectoris and of acute coronary occlusion is discussed in Chapters 11 18 and 21 respectively

CONTROL OF HYPERTENSION

General Considerations

Logical treatment of essential hypertension is handicapped by a lack of knowledge as to the etiology and pathogenesis of this disease If it is regarded as a generalized vascular disease rather than as a mere elevation of the blood pressure then little is known except that it consists in an increased constriction of the arterioles and the consequences thereof We do not know whether this arteriolar narrowing is due chiefly or exclusively to sympathetic vasomotor constriction or to intrinsic spasm initiated by humoral or metabolic agents or to an exaggerated arteriolar response to normally circulating constrictor substances Secondary structural changes may intensify the narrowing

We do not know whether or to what extent the elevation of blood pressure per se is responsible for the symptoms and complications of essential hypertension It is highly probable that the cardiac and cerebral complications which are the most frequent causes of death are due chiefly to atherosclerosis and that the elevated blood pressure is only a secondary contributory factor Furthermore many of the symptoms occurring in uncomplicated essential hypertension do not differ from those frequently seen in normotensive individuals with emotional disturbances On the other hand the elevated blood pressure per se appears to be a *significant if not the major* factor in the symptomatology and complications associated with that form of essential hypertension which is termed the accelerated or malignant phase [169] Despite occasional exceptions and moderate variations in the critical level of diastolic blood pressure associated with malignant hypertension clinical experience strongly indicates that the development of the fundus of malignant hypertension is associated with diastolic blood pressures of 140 mm Hg or more and that concomitantly with this elevation of pressure and fundus changes there develops a high incidence of

malignant nephrosclerosis with necrosis of arterioles uremia and the characteristic occipital headaches of recumbency and visual disturbances due to retinal hemorrhages and exudates

With these considerations in mind, the physician should decide whether he is treating or should treat an elevated blood pressure or a disease called essential hypertension In the group of cases termed malignant hypertension the reduction in blood pressure per se is an important therapeutic objective and the various specific blood pressure lowering agents or techniques are therefore indicated In all other groups of essential hypertension there is uncertainty as to the contribution of the elevated blood pressure to symptoms and complications and therefore there is a less definite foundation for the use of antihypertensive measures The use of measures to reduce the blood pressure in such cases may still be rationalized by the evidence that these elevations in blood pressure accelerate the development of coronary or cerebral atherosclerosis or add to the mechanical work of the heart It may be possible also that by lowering the blood pressure in the more benign group of hypertensive patients the malignant or accelerated phase will be prevented

It has already been indicated (see Prognosis) that an imperfect knowledge of the natural course of essential hypertension hampers a proper evaluation of those measures which claim to benefit the course of hypertension by reducing the blood pressure This uncertainty should be weighed when the physician recommends medical or surgical measures involving risk, expense annoyance and unpleasant side actions

Correction of Underlying Causative Disease

Remediable causes of hypertension should be sought Surgical removal of a pheochromocytoma or of a pituitary or adrenal cortical tumor correction of coarctation of the aorta (p 779) and relief of urinary obstruction may reduce or abolish hypertension When no adrenal tumor is found in a patient with hypertension due to Cushing s syndrome, the hypertension may be relieved by excision of one adrenal gland and about three quarters of the other [35] Unilateral nephrectomy occasionally offers a brilliant cure of hypertension, but the clinical history and the findings by pyelography or aortography should offer a strong probability that the unilateral disease is responsible for the hypertension before nephrectomy is undertaken [101] The function of the impaired kidney should be minimal or absent whereas the function of the remaining kidney should be relatively good and there should be no abnormal retention of nitrogenous material in the blood stream In 1918 Smith [illegible] found reports of 47 well documented cases in which a significant reduction in blood pressure was achieved among 242 instances of unilateral nephrectomy Schaffer and Markowitz[139] reported that more than one third of patients of all ages with hypertension and unilateral renal disease are rendered normotensive by nephrectomy, more than one third are unimproved and the remainder greatly improved

General Treatment

Adequate rest, relaxation and sleep are essential Occasional bed rest for a week or two may be valuable when the blood pressure rises to critical levels If there is severe headache elevation of the head of the bed with 12 inch blocks may be desirable during bed rest There should be no restriction of exercise recreation or other activities in the absence of complications Some physicians empirically prescribe moderate sodium restriction although only extremely low sodium diets effectively reduce blood pressure

Psychotherapy, including reassurance and readjustment of the patient's attitude and way of life, is valuable Some physicians who are "psychoanalytically oriented or who have a psychoanalytic bias would like to have the material under this heading dominate the section on treatment of essential hypertension However, despite the purported relationship between the stress of modern living and hypertension despite the psychopathologic personality said to be associated with hypertension and despite the fact that many of the symptoms of patients with hypertension are regarded as 'psychoneurotic" there is no scientific basis for attributing essential hypertension to psychic factors nor is there any valid evidence that hypertension can be alleviated or cured by psychotherapy On the other hand these comments should not be misinterpreted to mean that the patient with hypertension should not receive the benefits of psychotherapy when such treatment is indicated Psychoneurotic manifestations may be alleviated by psychotherapy in the hypertensive patient as in the normotensive Similarly, *mild sedatives,* such as the barbitu

rates bromides or chloral hydrate, are the drugs most widely used in hypertensive patients Perhaps this statement will require alteration as the newer hypotensive drugs begin to dominate therapy The sedative drugs like psychotherapy are indicated for the clinical symptoms and not for the reduction of hypertension per se But the Rauwolfia preparations may achieve a reduction in both emotional and vascular tension

Weight Reduction is desirable for the obese and is often associated with a fall in blood pressure [80] but in some studies the results are unpredictable inconstant and rarely impressive [1,2] Palmer[181] stressed the relation of obesity to hypertension and hypertensive vascular disease and recommended a low calorie diet which excludes all visible fat Despite the unproven relationship of obesity to hypertension the occasional beneficial influence of weight reduction on elevated blood pressure and the generally unfavorable effect of obesity on life expectancy [II] justify the recommendation of weight reduction in the obese hypertensive patient In evaluating the relationship of obesity and weight reduction to hypertension the physician should bear in mind the error introduced in the measurement of blood pressure in the obese[172] (p 921) The possible value of low calorie low fat (and presumably low cholesterol) diets to the hypertensive patient may be related to their alleged action in the prevention or retardation of the atherosclerotic complications associated with hypertension In addition weight reduction may be desirable because it may increase the cardiac reserve in hypertensive patients with early congestive heart failure

Specific Antihypertensive Measures

A number of specific measures are effective in reducing the blood pressure and modifying or alleviating some of the clinical manifestations in patients with essential hypertension These include (1) the rice diet and other very low sodium diets (2) the antipressor or hypotensive drugs (3) sympathectomy and possibly (4) bilateral adrenalectomy

RICE DIET AND OTHER LOW SODIUM DIETS[11]

The possible relationship of the sodium ion to hypertension has been discussed (p 923) Low sodium diets were recommended for the treatment of hypertension over 45 years ago[8] and recently regained temporary popularity The diets should contain preferably less than 200 mg but not more than 500 mg of sodium daily as described in the chapter on the treatment of heart failure (p 239) Adherence to the diet should be checked by determinations of urinary sodium which should total less than 500 mg in 24 hours Evidence has been adduced to show the value of extreme sodium restriction in the reduction of high blood pressure [II, 18]

Kempner[113] recommended the so-called rice diet (300 gm of rice 20 gm of protein but no animal protein 5 gm fat 150 mg sodium carbohydrates in the form of fruits or fruit juices to make 2000 calories 1 liter of fluid daily vitamin supplements) On this regimen Kempner observed a significant reduction in blood pressure in the majority of hypertensive patients as well as a decrease in the size of the heart a disappearance of electrocardiographic abnormalities and improvement or disappearance of retinal abnormalities

Recently Newborg and Kempner[143] reported on a follow up of 177 hypertensive patients with papilledema (malignant hypertension) 120 of whom were treated with the rice diet for 1 to 117 months There was a striking improvement in symptoms and signs of malignant hypertension with complete disappearance of papilledema in 92 of 100 patients who were able to adhere to the initial course of treatment There was an impressive increase in survival time during an average five year follow up period among those who adhered strictly to the dietary regimen e g of those who had followed the rice diet for at least a year and were continuing treatment 86 per cent were still alive compared with 19 per cent of survivals among those who discontinued the diet after the initial period of treatment The survival rate was significantly higher (70%) among those with good renal function than among those with impaired renal function (31%) as determined by the 2 hour phenolsulfonphthalein test

The essential findings of Kempner[114] and associates were confirmed by carefully controlled studies made by Watkin Froeb and associates[231] and by Corcoran and associates [37] who found significant reductions in blood pressure in 20 to 30 per cent of patients or more[1] on the rice fruit diet I have had similar experiences with patients who had adhered closely to the diet A period of 4 to [illegible] weeks on diets with adequately restricted sodium intake

may be necessary before there is a significant lowering of blood pressure

It has now been amply demonstrated that the merit of the Kempner rice-fruit diet depends on its very low sodium content [13, 44, 87, 94] Low sodium diets of more palatable and varied composition are as effective as the rice fruit diet in the reduction of high blood pressure On the other hand, the addition of small amounts of sodium to the rice fruit diet, causing the sodium content to exceed 500 mg or 1 gram reverses the fall in blood pressure which had been achieved by the rice diet The addition to the rice diet of protein fat and vegetables which were very low in sodium did not prevent the fall in blood pressure in individuals who were responsive to the rice diet [94]

The rice diet is an impractical method for the treatment of hypertension and is rapidly losing ground with the advent of the newer hypotensive drugs *Except for a few patients* in private practice or who are hospitalized, and except for those who are part of a group project supervised by an enthusiastic therapeutist it is impossible to maintain any large number of patients consistently and continuously on the rice diet This is due to its relative impalatability, its lack of variety and the omission of proteins and fat as well as salt These deficiencies have been partly met by very low sodium diets which are well balanced with respect to protein, fat and carbohydrates and which permit a variety of foods and spices other than salt But it is almost as difficult to maintain patients for long periods of time on such low sodium diets as are necessary to effect a reduction in hypertension

To reduce further the impalatability of extremely low sodium diets cation exchange resins have been proposed,[71] just as they have been used to improve low sodium diets in the treatment of congestive heart failure (p 244) With the aid of these resins, diets containing 1 to 1 25 gm of sodium (2 5 to 3 gm of sodium chloride) may be used instead of the levels of 200 to 500 mg which are ordinarily necessary Occasionally cation-exchange resin therapy in combination with low *sodium intake is followed* by dramatic improvement in patients whose hypertension had not responded satisfactorily to sympathectomy However the impalatability, bulk, expense and other unpleasant features associated with resin therapy have negated its advantages

The rigorously low sodium diet does not appear to be indicated in the mild or moderate form of hypertension On the other hand in the more severe types of hypertension, notably the malignant phase of hypertension the rice diet or equally restricted low sodium diets may be chosen for patients who will adhere strictly to the regimen and who will not or cannot tolerate the more powerful antipressor drugs and who prefer to try some form of medical therapy before considering sympathectomy In the presence of azotemia very low sodium diets may intensify renal insufficiency and may induce uremia[18] or the low sodium syndrome (p 275) Low sodium diets are beneficial in the patients with hypertension complicated by *congestive heart failure The rice* diet is a low fat, low cholesterol (as well as low *sodium*) diet and posses es whatever merit there may be in such a diet for the alleviation or retardation of the atherosclerotic complications of *hypertension* The low sodium diet may be preferable or safer than the strong hypotensive drugs in patients with cerebral coronary or renal insufficiency in whom there may be a risk of sudden reduction in blood pressure Finally, it is possible that low sodium treatment of hypertension has a *theoretical* advantage over the use of hypotensive drug and sympathectomy in that it may more directly affect the intrinsic arteriolar resistance which appears to be the basic abnormality in essential *hypertension* [177, 131]

DRUG TREATMENT OF HYPERTENSION

The drugs most widely used in recent years to reduce the blood pressure in hypertension are (1) Rauwolfia serpentina (2) Veratrum viride or album and their extracts or alkaloids (3) hydralazine (Apresoline), (4) the various autonomic ganglion blocking agent including the hexamethonium compounds pentolinium (Ansolysen) chlorisondamine (Ecolid) and mecamylamine (inversine) Essentially they act to reduce the blood pressure by diminishing the sympathetic vasoconstrictor tone of the arterioles Inhibition or release of sympathetic vasoconstrictor tone may not *represent* a correction of the basic pathologic state It may merely serve to reduce or eliminate normal vasoconstrictor tone and vasoconstrictor reflexes while the pathologic factor responsible for intrinsic arteriole constriction is unaffected The rationale of using these drugs is based on a presumed benefit from the reduction of arteriolar resistance and blood

pressure per se regardless of whether or not this reduction is accomplished by correction of the primary cause or basic mechanism

If hypotensive drugs are prescribed it is usually desirable to instruct the patient that he may experience possible unpleasant side actions until the dosage is adjusted over a period of weeks and how he may handle these side actions A member of the patient s immediate family or the patient himself is sometimes instructed in the technique of measuring the blood pressure and should be informed as to the variability in blood pressure readings and should be cautioned not to overemphasize minor elevations Multiple blood pressure determinations may be desirable during the course of the day with the patient in the standing as well as the recumbent or sitting positions When using drugs capable of inducing severe postural hypotension the patient s blood pressure should be carefully checked in the standing position or he should stand unsupported for one minute to determine whether he becomes faint or dizzy, before taking the next dose

The physician should start with the mildest hypotensive drugs and resort to stronger ones only when the former prove ineffective or when a considerable hypotensive effect is urgently required Similarly he should administer small doses and increase the dose gradually Sharp sudden reductions in blood pressure should be avoided because of the danger that hypotensive episodes may be complicated by coronary insufficiency and thrombosis by cerebral vascular insufficiency and thrombosis or by renal ischemia and shutdown The physician should be aware that blood pressure readings taken in his office may be significantly higher than those taken by the patient at home and that the latter may present [redacted] more useful guide to drug dosage

Choice of Drug

The decision to employ [redacted] hypotensive drug and the choice of drugs depend in large measure on the evaluation of the severity and type of hypertension and the presence or absence of complications as discussed above (p 930)

In practice the choice of hypotensive drugs for the treatment of hypertension may be discussed with respect to four groups of cases (1) the mild cases of benign hypertension (2) the moderate or severe cases of benign hypertension (3) the malignant or accelerated phase of hypertension and (4) various forms of hypertension associated with significant cardiac cerebral or renal complications

1 *Mild Benign Hypertension* In this type of patient with a systolic blood pressure under 200 and a diastolic pressure of 110 or less there is usually no indication for the use of hypotensive drugs Continued observation is desirable and conservative treatment consisting of reassurance mild sedatives and weight reduction if indicated One is less likely to administer hypotensive drugs if the hypertensive patient [redacted] female beyond the age of 45 than if a male or below the age of 45 In the latter groups the course of hypertension may become more serious and efforts to reduce the blood pressure are designed to prevent the development of higher levels of hypertension or more severe types If the patient is asymptomatic the physician has a problem in deciding whether to discuss the elevated blood pressure at all Since often some comment must be made in order to insure continued observation of the patient it is important to explain the nature of the elevated blood pressure and why active hypotensive treatment is not indicated if this is the physician s conclusion When non specific symptoms are present probably unrelated to the elevated blood pressure [redacted] such it [redacted] important to treat these symptoms by reassurance sedation and more formal psychotherapy if necessary In cases of mild hypertension with symptoms the preparations of Rauwolfia serpentina (p 939) have come to be widely used because they offer the benefits of mild sedation and at the same time are capable of reducing the blood pressure in a fair percentage of cases

2 *Moderate and Severe Benign Hypertension* In this group of patients with moderately or markedly elevated blood pressure but without the fundus changes which characterize malignant hypertension the systolic blood pressure is above 200 and may range to 2,0 or higher The diastolic pressure is above 110 and may be above 120 in the more severe cases For purposes of presentation we are omitting from this group patients with significant myocardial cerebral or renal complications The initial drug of choice in this group of cases would be a preparation of Rauwolfia serpentina because it is associated with the lowest incidence of side effects Dosage and method of administering the drug are discussed in detail below (p 940) If the Rauwolfia prepa

ration is ineffective or inadequately effective after several weeks a preparation of veratrum is added Subsequently a preparation of hydralazine may also be added if necessary, or it may be substituted for the veratrum if the latter was not tolerated As a rule I prefer not to begin with the ganglion blocking drugs, pentolinium Ecolid or Inversine in cases of hypertension not in the malignant or accelerated phase but I often employ them in combination with reserpine in patients with a fixed diastolic pressure of 130 mm Hg or more and in patients with Grade III fundus regardless of the degree of hypertension The administration of the ganglion blocking drugs is more complicated requires more careful observation and is associated with greater risk than the drugs which have been mentioned On the other hand if these other drugs alone or in combination are ineffective if the hypertension is severe or if the progress of the disease suggests the imminence of malignant hypertension or some serious complication, I employ one of the ganglion blocking agents preferably mecamylamine (Inversine) These drugs may be used alone or in combination with Rauwolfia or hydralazine (p 946)

3 Malignant Phase of Hypertension Despite the aversion of some investigators to the use of this term I am convinced that it has a useful and even valuable purpose But it is important that there be general agreement as to definition and criteria (p 930) In this group there is an urgent need for prompt reduction in blood pressure Hypotensive drugs are now first choice over the use of low sodium or rice diets or sympathectomy Hypotensive *drugs must be administered before there is* severe azotemia or uremia The primary hypotensive drugs for this condition are the ganglion blocking agents pentolinium Ecolid or Inversine As a rule they have been combined with Rauwolfia or hydralazine, which are designed to potentiate their effect to enable smaller doses of the ganglion blocking drugs to be used and to neutralize some of the side actions of these drugs The combination of a ganglion blocking drug with hydralazine or with Rauwolfia or with both may be undertaken from the beginning, or a maximal result may be obtained with either drug and the other drug added subsequently

If hypotensive drugs cannot be tolerated or are ineffective, the patient with malignant hypertension should be placed on a diet containing 200 mg of sodium or less preferably in combination with a Rauwolfia preparation alone or with Rauwolfia and veratrum in maximally tolerated doses If these measures are likewise ineffective, sympathectomy should be undertaken If the sympathectomy is likewise unsuccessful one should attempt to repeat the various hypotensive drug programs indicated because of the possibility that they will be effective after sympathectomy even though they were ineffective prior to that operation The possible application of bilateral adrenalectomy with and without sympathectomy is still under study With the use of the hypotensive agents, it appears that patients with malignant hypertension who ordinarily have a mortality between 85 and 100 per cent within 18 months to 3 years have had a mortality rate of about 45 to 55 per cent during a similar period The results are even more impressive when one considers only those patients with malignant hypertension in whom renal insufficiency is not advanced or is minimal

Many investigators do not favor the use of hypotensive drugs in patients with renal insufficiency, and this would appear to apply to many cases of malignant hypertension Although the course of malignant hypertension is rapid, there is a phase in which papilledema and high diastolic pressure are present but renal function is still relatively normal or at least compensated so that there is little or no azotemia During this phase of the disease and sometimes even when there is slight azotemia it is possible to reverse or retard the process by the use of these agents [104] In more severe cases *of hypertension with advanced renal insufficiency* it is probable that no form of therapy will be very useful and one must be satisfied with the administration of low protein diets and symptomatic treatment

4 Benign Forms of Hypertension with Complications. This concerns chiefly the cases of mild, moderate or severe benign hypertension with angina pectoris or coronary thrombosis with cerebral infarction or insufficiency due to atherosclerosis or cases complicated by uremia Most of the patients with hypertension terminating in uremia are in the category of the malignant phase In many instances in which cerebral or cardiac complications are present, these are due to atherosclerosis and not to the hypertension per se When the complication dominates the clinical picture

reserpine and those of serotonin, a vasoconstrictor substance isolated from the blood and brain and found chiefly in the small intestine, platelets and brain[24, 237] Reserpine, like serotonin, potentiates the sedative action of barbiturates and alcohol and is blocked by lysergic acid diethylamide (LSD) The administration of large doses of reserpine, as with serotonin, results in the prompt excretion of 5 hydroxy indole acetic acid (5 HIAA)

Indications Rauwolfia is utilized chiefly in the mild or moderate forms of hypertension and particularly in the labile hypertension of the so-called diencephalic type It is also widely used in combination with other drugs, particularly with the ganglion blocking agents Its stimulation of the bowel helps to combat the constipation caused by the latter It reduces the dose necessary for effective therapy and smoothes out the sharp fluctuations in blood pressure often caused by ganglion-blocking drugs Rauwolfia has been most useful in benign hypertension when administered in combination with veratrum and/or hydralazine It neutralizes the tachycardia and may prevent the headache caused by the latter The intramuscular or intravenous administration of reserpine has been used also to control hypertensive crises[102]

Dose and Administration The initial dose is 0.5 mg daily of reserpine (Serpasil) divided into one to four doses in the course of the day As a rule I start with 0.25 mg after the morning meal and again after the evening meal and continue for at least three to four weeks If there are unpleasant side actions (infra), then the dose is diminished to 0.1 mg twice daily If there is no effect I increase the dose in an effort to obtain a hypotensive action, but not more than 1 mg is given daily as a rule If increasing the dose produces unpleasant side actions without the desired effect, then the dose is somewhat diminished to eliminate the side actions and other drugs such as veratrum or hydralazine or eventually both, are combined with it (p 946) Since a satisfactory response may require four to six weeks, drastic changes in dosage and the addition of other drugs should be deferred until that interval has elapsed When used for the treatment of hypertensive emergencies reserpine is administered parenterally, but it is not as effective as veratrum or the ganglion blocking agents An initial dose of 2.5 or 5 mg is given intramuscularly or intravenously[79a] Thereafter 2.5 to 5 mg, occasionally up to 10 mg may be administered at 6 to 12 hour intervals but dosage is altered as required to obtain the desired blood pressure After a latent period of 1 to 4 hours a maximum reduction in blood pressure is attained 2 to 5 hours after administration[103] For more rapid effects veratrum hexamethonium or pentolinium should be employed

Results As the sole hypotensive drug Rauwolfia is usually effective only in mild or moderate cases of hypertension A moderate hypotensive effect is achieved in about half of the cases of benign hypertension and normal blood pressure may be restored in one third In addition it overcomes tachycardia when this is present Whether or not it reduces the blood pressure, it frequently relieves nervousness and anxiety, irritability, palpitation and headache According to some observers the hypotensive effect of reserpine is no greater than that to be expected from the use of a mild sedative and the establishment of patient rapport[141]

Side Actions The Rauwolfia preparations have virtually no serious toxicity and relatively infrequent and minor unpleasant side actions The commonest annoying side action is nasal congestion and stuffiness Antihistamine drugs appear to help this occasionally but have failed in most instances in my experience Sometimes this side action disappears with continued therapy Diarrhea or irritability of the bowel has been an annoying symptom in a few cases but generally this can be controlled by reducing the dosage It is not likely to occur when Rauwolfia is used in combination with ganglion blocking agents Similarly drowsiness, fatigability, increased appetite and weight gain, mental depression, apathy and occasionally unpleasant dreams or nightmares have been encountered but usually with large doses Rarely jitteriness or anxiety and, in men, decrease in libido without impotence have been noted Suicidal and paranoid tendencies have been noted rarely in patients on reserpine therapy A Parkinson like syndrome has been observed Perera described the occurrence of fluid retention with extensive edema and evidence of heart failure, following Rauwolfia therapy in occasional patients

Veratrum Compounds[130, 93, 137] *Preparations* These are drugs obtained from the roots of Veratrum album and Veratrum viride and are

composed largely of alkaloid esters yielding alkamines The preparation Vertavis is the crude root Vergitryl and Veriloid are purified mixed alkaloids of Veratrum viride, available in 1, 2 and 3 mg tablets Pure crystalline alkaloids protoveratrine A and B obtained from Veratrum album are marketed as Provell Maleate in 0 5 mg cross scored tablets and as Veralba in tablets of 0 2 and 0 5 mg Cryptenamine is an alkaloid fraction of Veratrum viride supplied commercially as Unitensin in 2 mg tablets [24]

Action The veratrum drugs reduce the blood pressure of hypertensive individuals by reflex depression of the carotid sinus and consequent inhibition of its effector vasoconstrictor nerves They produce cardiac slowing by a reflex mediated through the vagal cardio-inhibitory nerve The vasomotor center in the medulla as well as the carotid sinus may be involved in these reflexes The receptor sites of action for these drugs may be in the left ventricle coronary and pulmonary arteries The decline in blood pressure is associated with a reduction in the peripheral resistance which is evenly distributed through the vascular system and with a moderate decline in cardiac output [22] Veratrum compounds stimulate the emetic center (nodose ganglion) in doses which are fairly close to those producing the hypotensive effect

Indications The veratrum drugs were formerly used alone for their hypotensive effect but increasing tolerance and the small range between the hypotensive and emetic dosage minimized their usefulness At the present time they are indicated chiefly in combination with Rauwolfia or with Rauwolfia hydralazine for the treatment of mild or moderately severe cases of benign hypertension However their usage has diminished sharply The bradycardiac effect has been useful in hypertensive patients with tachycardia and in neutralizing the tachycardia of hydralazine Veratrum has been especially recommended for emergency use by intravenous administration in acute hypertensive crises (hypertensive encephalopathy) [120] and in hypertensive patients with acute heart failure

Dose and Administration The veratrum drugs may be administered orally intramuscularly or intravenously As a rule one begins with one tablet of any of the mentioned preparations (0 5 mg of Provell Maleate c~ ... or Unitensin 2 mg after each meal and again on retiring) In order to avoid gastrointestinal symptoms some investigators have tried to give the drug after an early breakfast four hours before the evening meal and on retiring The doses increase gradually one tablet per day at 3 or 4 day intervals until the desired hypotensive effect is achieved or unpleasant side actions occur As a rule 1 5 to 3 mg daily of the protoveratrine alkaloids (Provell Maleate or Veralba) or 8 to 14 mg of cryptenamine (Unitensin) is an adequate dose when the drug is tolerated Smaller doses may suffice and nausea may be less troublesome when combined with preparations of Rauwolfia The dosage must be carefully regulated by continuous trial in order to obtain the desired effect without disabling side actions

When used for *emergency treatment of acute hypertensive crisis* in essential hypertension glomerulonephritis or toxemias of pregnancy the drug is usually given intravenously Two mg of Veralba or Unitensin is dissolved in 200 cc of a solution of 5 per cent glucose in water or physiologic saline and administered by slow continuous drip beginning at the rate of 3 to 6 cc in 10 minutes The blood pressure is determined at frequent intervals When the desired reduction in blood pressure is obtained the rate of flow is slowed and regulated to maintain the effect Similarly protoveratrine has been given intravenously in an initial dose of 1 5 to 1 9 micrograms per kilogram of body weight with subsequent doses of 20 micrograms at 10 minute intervals until a satisfactory hypotensive result is obtained Intermittent intravenous injections may be given slowly in doses of 0 04 to 0 1 mg over a period of 5 to 20 minutes with frequent determination of blood pressure This may be repeated at 30 minute to 4 hour intervals with slight increments if necessary to obtain the desired hypotensive effect Veriloid has been administered intravenously at the rate of 0 6 to 1 1 microgram per kilogram of body weight per minute with reduction of blood pressure in all of 25 patients [314] A maximal response is usually attained within 30 minutes and the drug s action persists for 1 to 3 hours Acute excessive hypotensive effects may be treated by an intramuscular injection of phenylephrine (5 mg) and severe bradycardia may be overcome by the intravenous or intramuscular injection of 0 4 mg of atro...

reserpine and those of serotonin, a vasoconstrictor substance isolated from the blood and brain and found chiefly in the small intestine, platelets and brain[26, 237a] Reserpine, like serotonin, potentiates the sedative action of barbiturates and alcohol and is blocked by lysergic acid diethylamide (LSD) The administration of large doses of reserpine, as with serotonin results in the prompt excretion of 5 hydroxy indole acetic acid (5-HIAA)

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Veratrum Compounds[120, 98, 187] *Preparations* These are drugs obtained from the roots of Veratrum album and Veratrum viride and are

minimized by starting with very small doses of the drug, and usually subsides with continued treatment It is often alleviated by the administration of an antihistamine Tachycardia with palpitation also occurs relatively frequently A variety of other side actions has also been reported Among these dyspnea on exertion and anginal pain are particularly disturbing The anginal pain may resemble status anginosus Because of these side actions hydralazine should probably never be used in patients with hypertension complicated with angina pectoris or other clinical evidence of coronary heart disease

Apresoline may also cause dizziness faintness numbness or tingling of the extremities, malaise depression disorientation and anxiety Occasionally nausea and vomiting edema of the ankles and eyelids flushing nasal congestion lacrimation conjunctival injection skin rashes drug fever hiccups periosteal edema pain in the back of neck shoulders arms anemia pancytopenia and acute psychoses have been noted but most of these are relatively rare

After prolonged use of the drug particularly in high dosage (600 mg daily or more) rheumatoid arthritis with fever may appear And if the drug is continued, a syndrome resembling that of lupus erythematosus may develop[51, 167, 138, 96] In addition to incipient rheumatoid arthritis and fever there are pleural and pericardial manifestations skin rashes, microscopic hematuria occasional lymphadenopathy and splenomegaly, increased sedimentation rate altered distribution of serum proteins with an increase in gamma globulin leukopenia and L E cells Thus far it has appeared that a discontinuation of the drug has resulted in a satisfactory control of the syndrome The remission may be aided by the administration of corticotrophic hormones

Ganglion Blocking Agents (Hexamethonium[195, 203] Pentolinium[204] Ecolid[126, 40] Inversine)[65, 157] Hexamethonium compounds have had wide usage in the treatment of hypertension They are compounds with two quaternary ammonium groups connected by a 6 carbon chain *Hexamethonium chloride* was first administered chiefly by hypodermic or intramuscular injection in preparations containing 25 mg or 100 mg of the hexamethonium ion per cubic centimeter (e g Bistrium) The oral preparation is available as the bromide or chloride in scored tablets of 250 mg or 500 mg each (e g Methium, Esomid Hexameton) The hexamethonium preparations were largely replaced by *pentolinium tartrate* or pentamethylene pyrrolidium in which two terminal quaternary nitrogen atoms in pyrrolidine rings are connected by a chain containing 5 carbon atoms It is available commercially as Ansolysen in 20 mg, 40 mg and 100 mg scored tablets as well as in 10 cc vials containing 10 mg per cubic centimeter for subcutaneous or intramuscular use Still more recently similarly acting hypotensive drugs *chlorisondamine* (Ecolid)[174, 85, 1, 6] and *mecamylamine*[137] (Inversine) have been introduced Ecolid is a bis quaternary derivative of a dialkyl amino alkyl isoindoline At present Ecolid is available in 25 mg and 50 mg tablets for oral use Inversine a secondary amine (3 methylaminoisocamphane) is available in 2 5 5 0 and 10 mg tablets

Action These drugs are potent agents which suppress or inhibit both sympathetic and parasympathetic impulses by blockade of the ganglia of the autonomic nervous system Thus arteriolar constriction is diminished the peripheral resistance is reduced and the blood pressure is lowered Cerebral blood flow is diminished[35] Cardiac output may be initially increased but is then decreased Orthostatic reduction in blood pressure is especially marked and orthostatic hypotension may result from use of the drug The renal blood flow diminishes with fall in the mean arterial blood pressure despite a slight diminution in renal vascular resistance Cardiac rate is slowed and the force of cardiac contraction diminished Inhibition of parasympathetic impulses is responsible for many of the undesirable side actions (infra)

Although these drugs are essentially similar in their action they differ considerably in potency and duration of effect Pentolinium (Ansolysen) is said to be five times more active than hexamethonium in producing sympathetic ganglionic block whereas the less desirable parasympathetic ganglionic blocking effect is only one or two times that of hexamethonium Ecolid is likewise said to be five times as potent as hexamethonium The duration of action of pentolinium was found to be about 40 per cent longer than that of hexamethonium whereas the action of Ecolid is about five times as prolonged as that of hexamethonium Hexamethonium has a sig

nificant action usually for 2 to 4 hours, pentolinium for 8 to 12 hours or longer, reaching its peak in 2 to 4 hours, Ecolid acts for 16 to 24 hours and Inversine for 6 to 36 hours. As with hexamethonium, 20 per cent or less of the oral dose of pentolinium is absorbed after oral administration. Nevertheless pentolinium gave a more predictable hypotensive response, was more effective and better tolerated. In particular there was less constipation and interference with emptying of the urinary bladder with pentolinium. Occasionally uncontrollable sharp fluctuations in systolic blood pressure may occur with Ansolysen.

Ecolid possesses advantages over both pentolinium and hexamethonium because of better absorption and more prolonged action. The effects of Ecolid develop an hour or more after ingestion and reach a maximum in 6 to 8 hours, usually diminishing by 12 to 16 hours and disappearing after 24 hours. Because of the more prolonged action, fewer doses are needed than with either hexamethonium or pentolinium.

Inversine is superior to the other ganglion blocking drugs in that it is completely absorbed and is as effective orally as parenterally in equivalent doses. Its onset of action ranges between one half and two hours and its activity persists for 6 to 36 hours.[13]

Indications. The ganglionic blocking agents mentioned above are indicated in the treatment of severe forms of benign hypertension and especially in the malignant phase of hypertension. In the benign forms of hypertension, unless very severe, these agents should be used only after a trial of Rauwolfia preparations alone or in combination with veratrum and hydralazine has been found unsatisfactory. The ganglion blocking drugs are ineffective or contraindicated in the presence of uremia, but this should not be interpreted to preclude their use in cases of malignant hypertension with good renal function or with compensated renal insufficiency or minimal azotemia. These agents may be used in similar cases of hypertension which have not responded satisfactorily to the rice diet, extremely low sodium diets or sympathectomy. They may also be useful in the treatment of acute hypertensive crises, although protoveratrine has been generally preferred.

Dose and Administration. Hexamethonium has been administered intramuscularly or subcutaneously as the bromide or chloride salt, or given orally as the chloride.[93] It has now been largely replaced by the other ganglion blocking drugs.

Pentolinium (Ansolysen) replaced hexamethonium for oral use because of greater absorption, longer action, less tolerance and less constipation. The initial dose is 20 mg of Ansolysen three times daily. Smirk[93] has recommended that it be given on arising, between lunch and dinner, i.e., with the stomach empty, and before retiring, e.g., at 8 A.M., 3 P.M., and 10 P.M. But it has also been given after meals.[93] The dose is raised gradually every few days by increments of 20 mg if tolerated, until the systolic blood pressure of the patient in an upright position 2 to 3 hours after a dose of Ansolysen is 110 to 150 mm Hg. After a week, the patient may be receiving 100 mg three times daily, which is an effective hypotensive dose in many patients.[93] Some patients require only 40 to 60 mg or less three times daily, whereas other patients require 140 to 200 mg or more three times daily. In occasional instances the effective dose may go as high as 1 gm daily or more. Perry and Schroeder[165] reported an average daily dosage of 727 mg of pentolinium with 748 mg of hydralazine in 9 patients with malignant hypertension, and an average daily dose of 415 mg of pentolinium with 306 mg of hydralazine in 3 patients with severe benign hypertension.

It is important to individualize dosage according to the response and the occurrence of toxic symptoms. Furthermore it has been recommended that in patients over the age of 70 the initial dose be one third of that usually employed, and that it be half the usual initial dose in patients on a low sodium diet or who have previously had a sympathectomy. Dosage is controlled by frequent blood pressure determinations taken at home. The previous dose is cut in half if the standing systolic blood pressure is less than 120 mm Hg and omitted if less than 100 mm Hg or if there has been no bowel movement for 24 hours. The dose is similarly reduced or omitted if the patient experiences weakness, dizziness or faintness on standing upright for one minute just before each dose.

The dosage of *Ecolid* varies between 25 and 300 mg daily.[93, 126, 40] Initially the patient is given a 25 mg or a 50 mg tablet one hour before breakfast. This may act the entire day. However, if a second dose is needed, this is

given 1½ hours after the evening meal The second dose is determined by frequent measurements of the blood pressure at home The initial dosage of 25 mg is increased slowly by 25 mg increments until the desired effect is obtained Dryness of the mouth cycloplegia and constipation may be controlled by pilocarpine nitrate 5 mg three times daily, or by prostigmine bromide 15 mg one to three times daily A laxative may be necessary

Mecamylamine (Inversine) may be administered initially in 2 5 mg doses after the morning and evening meals and increased after a few days to 5 mg two or three times daily The dose is increased by 2 5 mg increments until a satisfactory hypotensive effect is obtained or side actions prohibit further increases Freis and Wilson[63] administered a mean daily dose of 30 mg (range 8 to 80 mg) to 35 patients with various grades of hypertension The mean reduction in basal blood pressure was 23 per cent systolic and 19 per cent diastolic in the supine position and 30 per cent systolic and 23 per cent diastolic in the erect position Because of increased morning reactivity to hypotensive drugs the morning dose should remain relatively small or be omitted and larger doses given after lunch dinner and at bedtime as required to obtain a smooth control of the blood pressure As with other ganglionic blocking drug therapy, the blood pressure should be taken with the patient standing and the dose should be omitted if there is dizziness or faintness on standing for one full minute Reserpine may be administered in combination with Inversine by giving 0 25 mg of reserpine morning and evening for several weeks and then only in the evening Inversine should probably not be used or used with caution to avoid intense and sudden hypotensive effects in hypertensive patients with severe coronary cerebral or renal insufficiency

The method of administering these ganglionic blocking agents with reserpine or hydralazine is discussed below

Results Ansolysen Ecolid and Inversine have not been used long enough at this writing to provide satisfactory follow up results But all three ganglionic blocking agents are capable of reducing the blood pressure in a great majority of cases of hypertension, including those with very severe benign hypertension and those with the malignant phase of the disease[196 203 83 137] Symptoms including severe headache are ameliorated Heart failure is controlled[112] In addition papilledema retinal exudates and hemorrhages when present, can be greatly diminished or eliminated the cardiac size reduced and electrocardiographic changes returned to normal

Follow up studies with hexamethonium have yielded very impressive results particularly in the treatment of malignant hypertension the natural course of which is best known and most unfavorable Schroeder[196] reported that in 212 cases of severe malignant hypertension that were adequately treated (with hexamethonium and hydralazine) and followed for a period of 13 to 34 months there was a 9 per cent mortality, whereas in similar patients discontinuing treatment the mortality was 60 9 per cent Furthermore the mortality rate due to known hypertensive complications was only 3 2 per cent in those who presented themselves without uremia and who continued treatment In those who discontinued treatment mortality from hypertensive complications was 55 per cent Of 68 patients with the malignant phase of hypertension 54 were alive after 13 to 34 months of treatment whereas 14 had died within a period of 1 to 18 months None of the 54 had malignant hypertension after treatment The mortality rate was only 3 per cent in those presenting without renal insufficiency, 11 per cent in those presenting with renal insufficiency and 100 per cent in those with previous uremia Similarly, Kaufman and Sokolow[110] in a 30 month follow up of patients with malignant hypertension who were treated with hexamethonium found that reversal of the malignant to the benign phase and survival beyond two years were possible in at least half of the patients who were treated while their renal function was still satisfactory These figures give striking support to the efficacy of treatment with these hypotensive drugs and also stress the importance of instituting treatment before uremia has developed

The early results with pentolinium give promise of at least equalling those with hexamethonium Gifford and associates[70] succeeded in reducing significantly the blood pressure of 23 of 24 patients with severe hypertension and satisfactory control was achieved for 1 to 7 months Among 27 patients with severe "fixed' hypertension with an average pretreatment blood pressureof

230/135 (range, 180/110 to 260/160 mm Hg) the blood pressure was reduced and stabilized at an average level of 170/110 (range, 130/95 to 210/130 mm Hg) following 2 to 6 months of treatment by Freis and associates[63] In a series of 31 cases treated with pentolinium tartrate there was a reduction of more than 20 mm Hg in the mean blood pressure in the standing position (median, 38 mm Hg) in 87 per cent and in the recumbent position in 67 per cent (median reduction 23 mm Hg)[2]

Similarly the early results with both Ecolid and Inversine indicate that these drugs are as effective as pentolinium in reducing hypertension and that their hypotensive action is smoother and more uniform throughout the day

Side Actions and Toxicity · One of the most important disturbances with hexamethonium resulted from the irregular and unpredictable absorption of the drug from the gastrointestinal tract with consequent cumulative effect This effect was particularly severe in the presence of constipation which is a regular side action of hexamethonium Occasionally the constipation has been so severe that ileus has resulted and has been fatal Excessive action after cumulation has resulted in sharp and sudden reductions in blood pressure with symptoms of postural hypotension or syncope and prolonged shock Other side effects include nasal stuffiness due to congestion blurring of vision due to loss of accommodation, dryness of the mouth and impaired sweating Anorexia urinary retention and impotence have also been annoying In patients under prolonged hexamethonium therapy, a fatal interstitial pneumonitis has been observed[45] perhaps more frequently in the Negro and in patients whose hypertension was poorly controlled by the drug

The side actions with pentolinium are essentially the same as with hexamethonium, except for lesser degrees of constipation, and similar side actions occur with Ecolid and Inversine However, constipation is much more severe with Inversine than with Ansolysen therapy Postural hypotension is particularly disturbing and may be characterized by weakness nausea, dizziness palpitation and tachycardia but especially by faintness or syncope Occasionally there is a sudden blackout and syncope without warning possibly resulting in injury The patient should be made aware that the peak action of Ansolysen is 2 to 4 hours after ingestion, and should be alert to assume the recumbent position if there are any warning signs I have observed prolonged hypotension and death from pentolinium Severe hypotension which does not respond to recumbency should be treated by intravenous Levophed[30] (p 563), until it is certain that the action of the pentolinium is completely dissipated (12 hours or more) Postural hypotension is also common with Ecolid and may be particularly troublesome in the early morning Blurring of vision associated with mydriasis, is especially disturbing because it may last all day Delayed gastric emptying with nausea or vomiting may occur initially Constipation, decreased force of micturition and dryness of the mouth have been noted but have been less troublesome than with the other ganglionic blocking agents

Side effects of Inversine include constipation, orthostatic dizziness and syncope, dryness of the mouth and occasional glossitis dilated pupils and blurred vision, decreased libido and potentia urinary retention, anorexia nausea vomiting, weakness, fatigue and sedation Fever, excessive heat infection, alcohol vigorous exercise and sodium depletion may be associated with excessive reaction to Inversine and other ganglion blocking drugs Pressor amines may be used to counteract hypotensive effects of Inversine but one should administer these cautiously Parasympathomimetic drugs such as neostigmine bromide, 15 mg, or pilocarpine nitrate 5 mg, may be used to overcome constipation, dryness of the mouth and some of the ocular symptoms

Combined Drug Therapy The use of combinations of the various hypotensive drugs discussed above has been mentioned repeatedly Some of these combinations may now be summarized When reserpine or hydralazine is combined with ganglion blocking agents it tends to reduce tolerance, diminish the required effective dose smooth out sharp fluctuations in blood pressure and neutralize or prevent some side actions[4]

Schroeder[195] has combined hexamethonium orally with hydralazine and termed this hyphex treatment After the oral hexamethonium dosage has been gradually increased to 500 mg every 4 hours or less if the desired blood pressure reduction has been obtained hydralazine is added in small doses (25 to 50

mg every 4 hours) with gradual increments until 150 mg per dose ■ given four times daily Thereafter the hydralazine is continued regardless of the blood pressure, but the hexamethonium may be increased up to 750 mg per dose or diminished according to need After the patient has been normotensive for about six months, the dose of one or the other drug ■ reduced gradually and then omitted When 1 mg of reserpine was added at night to hyphex therapy, the daily dosage of hexamethonium could be reduced in about one quarter of 75 patients

Freis[82] has recommended the simultaneous administration of Ansolysen with hydralazine and reserpine as well as neostigmine to neutralize constipating effects He gives these drugs in three dosage combinations which he terms hypotensen A B and C according to increasing strength of the dose These combinations all contain 0 ■ mg reserpine and 15 mg of neostigmine bromide but in addition A contains 20 mg of hydralazine and 60 mg of pentolinium B contains 50 mg of hydralazine and 100 mg of pentolinium whereas C contains 90 mg of hydralazine and 200 mg of pentolinium These combinations are put up in capsules The patient ■ started with one capsule of hypotensen A every 8 hours i e on arising in the morning in mid afternoon and at bedtime If after three days to a week there is no appreciable reduction in the blood pressure in the supine or erect positions hypotensen B is administered and at a later date if this is unsuccessful he is given hypotensen C Combinations of A B and C were also employed to adjust the dosage With these combinations Freis has claimed that there was little or no constipation minimal loss of visual accommodation dryness of the mouth or disabling postural hypotension But impotence remained a problem especially in older persons Similar results with pentolinium and hydralazine have been reported by Perry and Schroeder [163] More recently Doyle et al [47] and others ■ ■ have reported that the combination of reserpine with pentolinium is the best means of treating severe hypertension and this is the combination which I used most commonly until Inversine became available and replaced pentolinium

In mild and moderate cases of hypertension combinations have been used in which Rauwolfia serpentina preparations were the main stay If Rauwolfia therapy ■ not successful after a trial of 4 to 6 weeks ■ veratrum drug is added, one tablet being given three times daily after breakfast at 2 P M and at bedtime, i e at intervals of about 8 hours (one tablet of Provell or Veralba equals 0 5 mg) If after several days to a week there are no distressing side actions and if a satisfactory hypotensive effect has not yet been obtained the dose of veratrum may be increased to two three or four tablets three times daily until the desired effect is achieved without side actions Finally, if the veratrum and Rauwolfia combination is unsuccessful hydralazine (Apresoline) is gradually added beginning with 10 mg doses three or four times daily and increasing until the desired effect is obtained After a satisfactory hypotensive effect is obtained and drug therapy is continued for ■ matter of weeks or months it is possible to eliminate one or two of the drugs Wilkins and associates ■ reported that in about one third of 137 cases in which Rauwolfia and other drugs in combination were necessary to achieve ■ satisfactory reduction in blood pressure control was effected later by Rauwolfia alone Forty two of these patients still required both hydralazine and Rauwolfia and 16 required all three drugs Twenty-eight of the 137 had to have hexamethonium in addition to one or more of the other drugs Winsor ■ has reported that the combination of 0 4 mg of reserpine and 100 mg of Apresoline daily, in divided doses was most effective in benign hypertension Similarly Naegele and associates[14] found that the combination of Rauwolfia and hydralazine achieved an adequate reduction in blood pressure in most patients with mild or moderate blood pressure and frequently in those with severe hypertension Prior administration of Rauwolfia reduced the incidence and severity of palpitation tachycardia and headache commonly associated with hydralazine The latter was given in increasing doses up to 300 to 600 mg daily My own practice ■ to initiate treatment with reserpine and then to add Inversine to the reserpine in cases of severe benign hypertension or malignant hypertension Recently Eiber[52] reported satisfactory results with the combination of chlorpromazine and Rauwolfia in the treatment of hypertension Because of the hepatotoxicity of chlorpromazine and the availability of other effective drugs this combination appears undesirable for the treatment of hypertension

Other Drugs *Thiocyanate*[223] The argument as to the effectiveness and risk of toxicity of this drug has largely abated as it has been replaced by the newer hypotensive agents However, it is still used occasionally for the reduction of blood pressure in hypertension[5] and particularly for the control of hypertensive headaches[186] The oral daily dose is initiated with 0 3 gm but may be increased gradually by 0 15 gm per day up to 0 45 to 0 9 gm daily Blood levels of 8 to 12 mg per 100 cc should not be exceeded For relief of hypertensive headache it may be administered by intravenous injection of 20 cc of a solution containing 1 396 gm of sodium thiocyanate representing 1 gm of thiocyanate ion One may administer *sodium nitroprusside* orally to obtain the same effects as with thiocyanate The initial dose is 30 mg four times daily and this may be increased after a few days to 60 mg four times daily which usually gives a thiocyanate level of 8 to 12 mg For hypertensive crises sodium nitroprusside may be administered by constant intravenous infusion[195] A solution is made to give 100 micrograms per cubic centimeter and the infusion is started at the rate of about 100 to 300 micrograms (1 to 3 cc) per minute and modified according to the blood pressure and clinical response

Phenoxybenzamine hydrochloride (Dibenzyline)[151] This is a long acting adrenergic blocking agent which can produce marked postural hypotension as well as a reduction of blood pressure in the recumbent position[87, 8] However it has not proved satisfactory for the treatment of hypertension because of the difficulty in controlling the hypotensive effects because of tachycardia nasal congestion miosis, and especially because of the severity of weakness listlessness, dizziness, palpitation and other sequelae It is still indicated in the control of hypertension due to pheochromocytoma, in a dosage of 10 mg four times daily with gradual increases until the optimum effect is obtained It is usually stopped 36 to 72 hours before surgery, but may be utilized to control sudden rises in blood pressure during the course of the operation

Hydergine[11, 217] This drug contains equal parts of the hydrogenated alkaloids of ergotoxine, namely dihydroergocornine, dihydroergocristine and dihydroergokryptine These are powerful adrenergic blocking agents which have been recommended for clinical use in peripheral vascular disease and hypertension, especially in patients with cerebrovascular disease[215] Hydergine has not proved to be as useful in the treatment of hypertension as other agents mentioned above and has attained no popularity in this country[50] Lowering of blood pressure in hypertensive patients has been too inconstant and of relatively small degree

Pyrogens and specifically soluble bacterial pyrogen (Pyromen—Baxter), administered intravenously 5 or 6 days weekly in a sufficient dose to cause a temperature rise to 103 or 104° F , were reported to induce a reversal of the malignant phase of hypertension to prevent uremia and prolong life in these patients[150] Similar effects have been claimed for the ganglion blocking agents, rice diets and sympathectomy, which are more practical

SURGICAL TREATMENT OF HYPERTENSION

Sympathectomy

More or less extensive sympathectomies have been performed to eliminate or reduce the neural component responsible for increased splanchnic, arteriolar vasoconstriction in hypertension More probably these operations reduce arteriolar constriction by diminishing normal sympathetic tone without affecting the pathologically increased intrinsic arteriolar tone Peet performs a bilateral supradiaphragmatic splanchnicectomy and lower dorsal ganglionectomy in a single stage procedure[188] Smithwick[208] performs a bilateral lumbodorsal splanchnic sympathectomy, removing the great and lesser splanchnic nerves dividing their aortic branches, excising the sympathetic trunk and interrupting their rami communicantes from D6 to L2 The operation is performed through a posterior, transdiaphragmatic approach in two stages usually with a ten day interval between stages An even more extensive sympathectomy is carried out by Grimson[80, 82]

Beneficial and sometimes striking results have been reported in a majority of operated patients with these procedures[188, 100, 32, 210, 11] Reduction in blood pressure, disappearance of severe retinal abnormalities with improvement or return of vision, elimination of intractable headache and restoration of gainful occupation have been noted frequently or almost regularly A reduction in blood pressure has been reported in 21 to 66 per cent of various series of operated cases A prolongation of

life for patients in the serious malignant phase of hypertension has also been reported [157] It is interesting to note the frequent reversal or disappearance of cardiac abnormalities including cardiac enlargement electrocardiographic evidence of left ventricular hypertrophy as well as gallop rhythm, pulsus alternans and recurrent left ventricular failure [75, 157, 107] It is of interest also that the results obtained from the less extensive procedures of sympathectomy are almost as good as those obtained from the more extensive procedures which most advocates of sympathectomy favor for the highest percentage of favorable results

Smithwick and Thompson[110] compared the results of splanchnicectomy for essential hypertension in 1266 patients who had a thoracolumbar sympathectomy with the results in 467 patients who were suitable for operation but refused it The over all five year mortality was 19 per cent in the operated group and 54 per cent in the non operated The operative mortality varied from zero in group I to 11 per cent in the most severe group group IV At the end of five years the mortality in each of the groups was considerably lower in the operative series than in those refusing it The most striking difference was observed in group II with a 13 per cent mortality in the operated patients and 38 per cent in those who were not operated on and in group III in which the mortality was 20 per cent in the operated and 71 per cent in the non-operated In group IV corresponding most closely to the cases termed malignant hypertension the mortality was 59 per cent in the operated patients at the end of five years compared to a mortality of 90 per cent in the non operated Smithwick *and Thompson considered sym*pathectomy to be the treatment of choice for hypertension in the cases falling in groups II and III, although some of the patients in these groups required treatment by diet and drugs as well It is of interest that the most striking improvement was noted in those groups of patients in which it is most difficult to be sure of the natural course of the disease without operation There is considerable question whether the non operative cases classified in corresponding groups can be accepted as adequate controls Although the results in group IV are reported as being less dramatic they are more impressive to me because the reduction in mortality occurred in a group of patients in whom we are reasonably certain that an unfavorable course would have ensued

The operation has been criticized as being at most a palliative procedure of desperation of unproven advantage over medical therapy unphysiologic and without effect on the basic cause of hypertension [75] A significant persistent reduction in blood pressure is obtained in less than 50 per cent of those operated on [109] Disadvantages include an operative mortality of 1 to 5 per cent or more considerable postoperative morbidity a relatively long period of hospitalization and convalescence in the Smithwick procedure annoying postural hypotension for several months neuritic pain for months, frequent loss of ejaculation in the male but not impotence and uncomfortable sweating in areas supplied by the unoperated sympathetic fibers In addition one must stress the failure to obtain a satisfactory reduction in blood pressure in at least 30 and possibly 70 per cent of the operated cases and the fact that even when hypertension is initially controlled the reduction in blood pressure and other effects is maintained in probably not more than 20 per cent in a period of three years The operation is contraindicated in the presence of azotemia very recent myocardial infarction or cerebral accident and uncontrolled heart failure On the other hand alleviation of the hypertensive factor may eliminate the manifestations of heart failure as well as other clinical complications

The surgical indications vary with different physicians Sympathectomy has been largely abandoned as a treatment for hypertension in most clinics since the introduction of low sodium diets and especially the hypotensive *drugs For the most part sympathectomy* is now reserved for patients with severe and progressive manifestations especially those with the malignant form of hypertension who do not respond to medical therapy as outlined above

Taking cognizance of the powerful effects and frequent side actions of the recent hypotensive drugs especially the ganglion blocking agents Proger[175] has properly raised the question whether sympathectomy especially a simple superdiaphragmatic splanchnicectomy as advised by Peet may not be a more conservative method of treating hypertension than the lifelong use of the hypotensive drugs

However it is apparent that after having been employed for about twenty years, sympathectomy is rapidly falling into disuse This clearly indicates that the surgical procedure of sympathectomy despite its relatively low mortality is regarded as a formidable experience in comparison with available medical regimens and that the results obtained by the latter are regarded as being at least as satisfactory as those obtained with sympathectomy

Bilateral Adrenalectomy

Total and subtotal adrenalectomy, alone or combined with sympathectomy, have been utilized in the treatment of severe hypertension by several groups of investigators [41, 6, 73, 240, 105] The rationale for the procedure was based on the experimental and clinical observations relating the adrenal gland to hypertension (p 923) and upon the observations of Green et al [79] that bilateral adrenalectomy was followed by prolonged regression of vascular disturbances in a diabetic patient with malignant hypertension An operative mortality of about 25 per cent in the earlier cases has been considerably reduced to about 3 to 10 per cent Since Addison s disease is produced by the operation, 25 to 50 mg of cortisone or its equivalent in related steroids 3 to 6 gm of sodium chloride and approximately 2 mg of desoxycorticosterone acetate (Doca) must be given daily Bowers [2] performs a bilateral adrenalectomy in two stages two weeks to three months apart The operation was performed or attempted in 27 patients Six patients died in the immediate postoperative period A normal blood pressure was restored in 20 of the 21 survivors Symptomatic improvement of hypotensive symptoms was obtained in all the survivors Hypoadrenalism was present in all The reduction in blood pressure was maintained for as long as 22 months at the time of the report

Jeffers and associates[105] reported on adrenal resection and sympathectomy in 125 hypertensive patients, in 96 of whom an Adson type sympathectomy and either total or subtotal adrenalectomy were performed The mortality rate was 23 per cent for a four year period Death was due to strokes in more than one half of the cases and to coronary occlusion uremia and adrenal insufficiency in many others In those who survived, the reduction in blood pressure was interpreted as excellent in 44 per cent, fair in 24 per cent, and improvement was described in the fundus, size of the heart, electrocardiogram and especially in symptoms of congestive heart failure Headache and angina pectoris were relieved in 70 per cent

In the light of the comments regarding sympathectomy it is difficult to believe that this even more extensive surgical procedure will gain acceptance as a form of therapy I is uncertain whether the results are any better than those of sympathectomy alone And this procedure, as has been stated, is being rapidly replaced by medical forms of therapy It is generally stated that adrenalectomy is still an experimental procedure for hypertension and should only be used as such This operation may be indicated occasionally when a patient with malignant hypertension cannot be controlled by any medical means or sympathectomy It may also be indicated in forms of hypertension associated with Cushing's syndrome It is contraindicated in patients with poor renal function or azotemia, in patients who have suffered a coronary occlusion or cerebral vascular accident less than six months earlier and in patients more than 55 years of age [105]

THE HEART IN RELATION TO RENAL DISEASE

ACUTE GLOMERULONEPHRITIS

There are four important manifestations of acute glomerulonephritis which are of special interest to the cardiologist (1) hypertension, (2) cardiac enlargement, (3) electrocardiographic evidence of myocardial involvement and (4) congestive heart failure

Hypertension is a cardinal feature of acute diffuse glomerulonephritis and occurs at the onset of the disease The rise in blood pressure is almost always moderate and usually does not exceed 180/100 except with encephalopathy

Cardiac enlargement appears early probably within the first week or two [28, 119] The enlargement is relatively mild but may be considerable in the presence of pronounced congestive heart failure Serial roentgen ray examinations disclose a return to normal cardiac size with subsidence of the disease [41] Occasionally cardiac enlargement persists despite normal blood pressure [58] Hypertrophy

as well as dilatation of the left ventricle is observed at autopsy[268]

The cardiac enlargement has generally been attributed to the hypertension but it has been observed in the absence of significant hypertension and the degree of enlargement is usually out of proportion to the mild elevation in blood pressure and its brief duration Gore and Saphir [redacted] found evidence of a serous myocarditis with sparse cellular infiltration in 16 of 160 anatomically proven cases of acute and subacute glomerulonephritis They attributed both cardiac hypertrophy and failure to the myocarditis On the other hand I have observed pronounced cardiac enlargement and hypertrophy only in association with heart failure and it has appeared to me that it is the heart failure which, in accordance with Starling s law of the heart, is responsible for the enlargement

Electrocardiographic abnormalities occur frequently but they are mild and may not be observed except after repeated examinations Low or inverted T waves in lead I and in the precordial leads are the commonest changes [78, 245] Prolongation of the P R interval and of the Q T interval also occurs According to La Due and Ashman[277] right deviation of the Wilson gradient is a common abnormality and denotes relative ischemia of the left ventricle The electrocardiographic changes are not necessarily indicative of anatomic myocardial damage but may be due to such factors as hypertension cardiac enlargement and electrolyte and acid base disturbances The electrocardiographic abnormalities usually disappear within two to four weeks

Congestive heart failure is the most important most serious and most frequent complication of acute glomerulonephritis[260, 307, 291, 250, 289] It has been reported to occur in 20 to 50 per cent of the latter A diagnosis of cardiac failure was established in 22 of 88 cases recently reported by Murphy and Murphy[289] Heart failure has been attributed to the strain of the hypertension[276, 289] and to myocardial damage as indicated by electrocardiographic and anatomic changes But the elevation in blood pressure appears too slight and brief and the electrocardiographic and anatomic changes too minor to be significant and there is often no correlation between the degree of hypertension and the presence or severity of heart failure[291, 307, 255] The heart failure appears to me to be due to a relative deficiency in the renal excretion of sodium and water[256] It appears most frequently when oliguria is severe and is usually induced by overenthusiastic parenteral administration of sodium containing fluids to combat vomiting and promote diuresis Although acute glomerulonephritis is regarded as primarily or predominantly a glomerular disease tubular function in this condition is disturbed to a variable degree and tubular disturbance may be as severe as in the so-called lower nephron nephrosis (p 952) The clinical picture may be indistinguishable from the latter and the dangers of sodium and fluid administration are just as great in the presence of severe oliguria This explanation does not exclude the possibility that hypertension and myocardial edema— serous myocarditis —are secondary accessory factors in the accentuation of myocardial disability[285]

Heart failure may be characterized by a sudden onset of dyspnea and orthopnea often progressing to acute pulmonary edema But frequently it appears more gradually Tachycardia muffled cardiac tones an apical systolic murmur gallop rhythm and râles at the bases of the lungs are common with left ventricular failure But heart failure may develop more insidiously and may involve the systemic as well as the pulmonary circulation Pleural effusion is common and is part of the general anasarca There is evidence that renal edema fluid does not differ essentially in composition from that of cardiac edema and may have a similar pathogenesis[305] A high venous pressure was found regularly by several observers[276, 255] but the circulation time was normal The blood volume is usually increased[75] Davies[55] found the cardiac output normal in 5 patients with acute glomerulonephritis studied by cardiac catheterization The explanation for the normal circulation time in the presence of ' congestive heart failure in nephritis is uncertain It suggests that some associated factor is neutralizing the circulatory slowing usually associated with heart failure or that there was no cardiac failure but only an abnormal retention of sodium and water However the circulation time may be prolonged when heart failure complicates acute glomerulonephritis as I have observed on several occasions and as reported by Kopelman[274] The edema of nephritis like that of heart failure may not be caused by an intrinsic disturbance in capillary permeability, but by an elevated

hydrostatic pressure, sodium and water retention and sometimes also a diminution in osmotic pressure due to low plasma proteins

Treatment

The treatment of acute glomerulonephritis should be primarily directed to the prevention or abolition of heart failure, which is always present or a potential danger Sodium intake should be completely avoided if there is severe oliguria and should not exceed 200 mg daily until normal urinary output and concentration are restored The parenteral administration of fluids is hazardous until that stage is reached During the acute phase an allowance of 500 to 1000 cc of fruit juice orally, is permissible as the total diet In the presence of severe oliguria or anuria fluid intake must be stringently restricted Thereafter one may shift to the rice-fruit-fruit-juice regimen as advocated by Kempner until renal function is restored In the presence of heart failure, digitalis in a rapidly excreted form should be given (e Cedilanid Digoxin) Mercurial diuretics should not be administered Acute left ventricular failure with pulmonary edema should be treated by morphine oxygen intravenous digitalization, application of tourniquets and if necessary, phlebotomy

TOXEMIA OF PREGNANCY (PREECLAMPSIA AND ECLAMPSIA)

The findings in the heart and circulation in toxemia of pregnancy resemble very much those described for acute glomerulonephritis [301] Edema, indicated by too rapid weight gain in the last three months of pregnancy, hypertension proteinuria and sometimes oliguria are the essential clinical features of preeclampsia, and eclampsia denotes that convulsions and/or coma are also present Sodium and water retention account for many of the cerebral, visual, renal and gastrointestinal symptoms Cardiac failure especially pulmonary edema, is due to excessive sodium water retention, but hypertension may be a contributory or major causative factor Studies with radioisotopes have indicated a progressive increase in the sodium space and in total exchangeable sodium during the course of pregnancy, but this increase is quantitatively greater in those who develop preeclampsia [67]

Treatment

Limited caloric intake and especially restriction of sodium to less than 1 gm daily in the last three months of pregnancy are indicated at the earliest signs of too rapid gain in weight or rising blood pressure Mercurial diuretics, with or without ammonium chloride may be administered, but their effectiveness in causing a diuresis is usually less striking than in the usual forms of congestive heart failure If the patient is in acute pulmonary edema morphine, oxygen, intravenous digitalization and possibly phlebotomy may be necessary If the patient is observed in a hypertensive crisis (hypertensive encephalopathy) with severe headache, vomiting cerebral amaurosis, aphasia or focal paresis with or without convulsions a hypotensive drug should be given intravenously, , veratrum as indicated on page 941 The patient should be in a quiet room and given adequate sedation, if necessary Convulsions should be controlled by 6 to 12 cc of 50 per cent magnesium sulfate injections intramuscularly or by a slow intravenous drip of 250 cc of 2 per cent magnesium sulfate, and by parenteral injections of sedatives (e g , 0 25 Sodium Amytal subcutaneously or the slow intravenous administration of 0 5 gm Pentothal sodium or Sodium Amytal) But sedatives should of course be avoided if the patient is comatose

If conservative treatment controls the "toxemic" manifestations, delivery should be induced at the earliest possible time compatible with the safety of the mother and child Termination of pregnancy is the single most reliable therapeutic measure in "toxemia" Immediate termination of pregnancy becomes particularly mandatory if symptoms of preeclampsia are very severe and not satisfactorily controlled if eclampsia develops, or if there are complications such as abruptio placentae

In many cases of so-called "toxemia of pregnancy" there is actually an underlying or preexistent essential hypertension or chronic glomerulonephritis Hypertension and proteinuria may become intensified during the course of pregnancy, or preeclampsia or eclampsia may be superimposed The hypertensive crises and cerebral edema of eclampsia may be indistinguishable from the hypertensive encephalopathy of essential hypertension

LOWER NEPHRON NEPHROSIS

Under the heading of lower nephron nephrosis [30, 282] are included renal diseases characterized by tubular degeneration and necrosis with subsequent regeneration fre-

quent pigment deposits in the tubules and interstitial inflammation but no visible glomerular alterations. Other terms for this condition include crush syndrome,[51, 52] acute anuria,[29, 47] acute tubular necrosis,[59] and shock kidney.[304] The tubular injury causes excretory failure with loss of tubular regulation and indiscriminate or virtually complete reabsorption of the glomerular filtrate.[95, 300] The disease may be caused by a wide variety of agents which induce prolonged shock, renal ischemia and anoxia or allergic and toxic damage to the tubules.[292, 304] Some of the best known causes are (1) extensive burns[34] or wound shock, especially the crush syndrome;[261, 258] (2) hemoglobinuric nephrosis due to mismatched blood; (3) sulfonamides;[283] (4) carbon tetrachloride inhalation;[290, 2, 5, 64, 295] (5) blackwater fever and other factors responsible for intravascular hemolysis of erythrocytes; (6) hyperthermia and various poisons and any condition which causes an acute prolonged reduction in cardiac output and shock,[59, 304] and consequent ischemia and anoxia of the renal tubules.

From the cardiovascular viewpoint the important features are the acute development of extreme oliguria or anuria and hypertension and the invariable danger and frequent occurrence of congestive heart failure. Cardiac dilatation, gallop rhythm, pulmonary congestion and hydrothorax, subcutaneous edema and ascites are common. Death is often due to acute pulmonary edema. Almost invariably the development of heart failure is precipitated by the parenteral administration of fluids in an effort to alleviate vomiting, promote diuresis, correct acidosis or maintain fluid or electrolyte balance. Intracellular breakdown contributes extensively to the excess of extracellular volume. Both of these factors are important because there is no urinary output at all or only an insignificant amount. Similar clinical evidence of left ventricular failure may be precipitated by parenteral sodium-containing fluids in patients with toxemia of pregnancy[373] whose urinary output is very small.

Treatment[19, 249, 267, 300, 7, 238]

Treatment should consist of no more than 500–750 cc. of fluids by mouth if tolerated. Or other forms of sodium free carbohydrate and fat diets such as Borst's butter and sugar diet[244] designed to minimize protein catabolism and maintain caloric intake, may be employed. The parenteral administration of fluids is interdicted until there is a good urinary output and improving renal concentration with a falling blood urea. Intravenous administration of fluids, even in limited amounts intended to compensate for insensible perspiration and vomited fluids, may be dangerous because of previous excessive fluid or sodium intake and because of shifts of fluid from the intracellular to the extracellular compartment. Peritoneal irrigation,[308, 290] artificial kidney[7, 287, 73] or similar therapies[93, 54, 69, 367] may be considered during the period of anuria and extreme azotemia. As a rule these are unnecessary except in the presence of significant hyperkalemia[97] or to control serious fluid retention. Johnston et al.[369a] claimed beneficial effects in cases of acute renal failure caused by ischemia from the intramuscular administration of the vasodilator drug papaverine (32 mg. every 2 hours for 48 hours).

When diuresis occurs, fluid intake may be increased cautiously, but the intake of sodium or of protein foods must be restricted until it is apparent that urea clearance and electrolyte excretion are adequate and blood urea nitrogen is diminishing. In the presence of oliguria or anuria digitalis should be given cautiously even when heart failure is present. Cedilanid by injection or Digoxin orally is preferred because of rapid elimination, but the usual dosage should be diminished to allow for deficient excretion. Mercurial diuretics are interdicted.

In some instances, if the patient is seen early during the stage of shock and if there is a low blood volume, the cautious administration of blood, plasma or saline is indicated. When oliguria is the result of dehydration caused by excessive vomiting or diarrhea or diabetic acidosis, the urine is almost always concentrated before renal tubular failure has occurred and there is usually little risk in the vigorous replacement of fluid and electrolytes. The urinary output should increase promptly. On the other hand, when oliguria is already present following prolonged shock and the urine is dilute and of low specific gravity (except when grossly bloody), there is great danger of overhydration in administering blood or fluids in an effort to overcome shock.

As a rule lower nephron nephrosis is a spontaneously reversible condition in which diuresis begins several days to two weeks after onset

and clinical improvement follows, provided that the patient does not succumb from heart failure pulmonary edema or hyperkalemia as a result of improper treatment Several months may be necessary for complete recovery of renal function Occasionally renal recovery is incomplete

CHRONIC NEPHRITIS AND UREMIA

Cardiac manifestations are uncommon until the stage of advanced renal insufficiency and uremia [93] Hypertension is less prominent than in cases of essential hypertension but occasionally the blood pressure and clinical features are indistinguishable from those of the malignant phase of essential hypertension is often a terminal manifestation, it may appear many weeks before the end, may undergo remission and recurrence and may even heal [271] Extreme retention of potassium may cause ventricular standstill or fibrillation and death [93]

The heart in uremia may show not only pericarditis but also foci of fatty degeneration and vacuolization of muscle fibers, which have been likewise attributed to metabolic toxins [[illegible]] Lüscher[281] described a case in which there was severe interstitial hemorrhagic myocarditis

Roentgen ray films of the chest show no abnormality or the left ventricular enlargement associated with hypertension Occasionally there are striking pulmonary changes



Fig 144 Azotemic edema of lungs *A* Glomerulonephritis with azotemia and pulmonary edema "Butterfly" type of pulmonary congestion and edema Symmetrical densities fan out from hila like wings of a butterfly Heart enlarged
B Clearing of lung fields and reduction of cardiac silhouette in same patient after treatment

Coronary atherosclerosis is less frequent than in essential hypertension probably because most patients with chronic glomerulonephritis succumb before the age of 40 In the cases of nephritis with hypercholesterolemia the coronary atherosclerotic process is said to be precocious

Heart failure is uncommon except toward the end of the disease It results from deficient excretion of sodium and water the intravenous administration of excessive quantities of fluids and occasionally from associated hypertension coronary atherosclerosis and anemia

In the presence of *uremia*, a sterile pericarditis occurs, possibly due to retained metabolites [99] (p 601) While the pericarditis characterized by bilateral clouding of the central and lower median lung fields which may appear and disappear in a few days (azotemic edema of the lungs) [2 3] (*Fig 144*) They are due to pulmonary edema caused by left ventricular failure

Electrocardiographic changes occur often in uremia There are frequently evidences of left ventricular hypertrophy and of myocardial damage in the cases associated with severe hypertension and coronary atherosclerosis More distinctive are [[illegible] 302]

(1) T wave inversions with or without ST elevations due to diffuse pericarditis [271]

(2) Prolongation of the Q-T interval due to hypocalcemia,

(3) Tall narrow T waves in limb and chest

leads with early hyperpotassemia bizarre slurring notching and widening of the QRS complexes[270] and bradycardia with or without intraaterial and atrioventricular block with more advanced potassium intoxication and finally cardiac arrest[221] ■ Electrocardiographic changes of hypopotassemia (p 1031) may occur in chronic renal insufficiency[103] as a result of vomiting diarrhea and insufficient food and therefore low potassium intake[296] (prolonged Q T interval wide T wave depression of ST segment)

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Chapter 38

PULMONARY EMBOLISM AND ACUTE COR PULMONALE

RELATION OF PULMONARY EMBOLISM TO HEART DISEASE

The occurrence of pulmonary embolism following operation is well known but it is less generally recognized that it appears with greater frequency among medical patients,[4,5] especially those with heart disease[6,7] Thus of 370 autopsied cases of pulmonary embolism and infarction Hampton and Castleman[8] found that 40 per cent represented a post operative complication, but 30 per cent were cardiac medical cases and another 30 per cent non-cardiac medical cases

Pulmonary embolism is of special interest to the cardiologist in the following relationships

1 **Congestive Heart Failure** Pulmonary embolism may precipitate congestive heart failure in the cardiac patient especially the rheumatic cardiac who was previously well compensated It is a frequent cause for intensification of congestive heart failure and very commonly it is responsible for refractoriness of heart failure to all therapeutic agents Finally, it may be responsible for sudden death or it may represent the final blow in a chronic progressive unfavorable clinical course of patients in heart failure

2 **Acute Myocardial Infarction** (p 541) Pulmonary embolism is a common complication and is an important cause of death in the fatal cases of acute myocardial infarction Not infrequently pulmonary embolism presents a problem of differential diagnosis from acute myocardial infarction especially in patients with previous coronary occlusion Pulmonary embolism may itself be responsible for acute myocardial necrosis in the absence of acute coronary occlusion especially in the presence of preexistent coronary narrowing or occlusion

3 **Rheumatic Heart Disease** Pulmonary embolism has presented a problem in patients with rheumatic heart disease, and specifically mitral stenosis who are being considered for mitral commissurotomy Frequently they develop fever, without apparent cause which is interpreted as evidence of active rheumatic fever This is responsible for prolonged delay in performance of the operation or for rejection of the patient as unsuitable The actual cause of such fever is usually *recurrent pulmonary embolism* or occasionally patchy bronchopneumonia in the congested lung Although there is pathologic evidence suggesting the frequent presence of "active" rheumatic inflammation in the adult patient with rheumatic mitral stenosis this cannot be related to overt clinical manifestations of rheumatic activity Rheumatic fever is rarely responsible for acute febrile disease in the adult patient (over 25) with mitral stenosis and heart failure

4 **Unexplained Fever in the Cardiac Patient** Pulmonary embolism is the commonest cause of unexplained fever in the adult patient in congestive heart failure or in the cardiac patient who is subjected to bed rest for any reason In the adult with compensated rheumatic heart disease or congenital heart disease, bacterial endocarditis is the commonest cause of unexplained fever lasting more than a week In the child with a previous history of rheumatic fever rheumatic activation is the commonest cause of protracted fever but usually there will be other signs besides the fever

5 **Chronic Cor Pulmonale** The occasional development of chronic cor pulmonale due to recurrent pulmonary embolism will be discussed (p 981)

6 **Acute Cor Pulmonale** This includes cases of sudden pulmonary vascular obstruction due to massive or extensive pulmonary emboli Acute cor pulmonale and pulmonary em

bolism are not interchangeable terms, for only massive or extensive embolization is usually capable of producing cardiac disease

ETIOLOGY OF PULMONARY EMBOLISM

Pulmonary emboli result from dislodgment of antemortem blood clots arising in a thrombus of the systemic veins or right chambers of the heart As a rule the embolism is of the bland (non infected) variety Complete bed rest with immobilization of the body is the most important factor associated with venous thrombosis and consequent pulmonary embolism Cardiac disease, especially when complicated by heart failure malignant disease, especially of the pancreas, hematologic disease especially polycythemia obesity, age above 50 and varicose veins are among the predisposing factors[48, 8] Pulmonary embolism occurs after operations especially in the pelvic organs in females after prostatectomy in the male after parturition and after immobilization for fractures or for cerebrovascular accidents[8]

Pulmonary embolism is commonly precipitated by factors which raise the venous pressure and thus dislodge a venous thrombus e g, straining at stool getting out of bed or getting in and out of a wheelchair[70, 64]

PATHOLOGY

Pulmonary embolism may result from venous thrombi associated with pain, redness and swelling classified as *thrombophlebitis*,[2] or from venous thrombi which are virtually asymptomatic and classified as *phlebothrombosis*[1, 38, 34]

The source of the pulmonary embolus is a thrombus, almost always in the veins of the lower extremities but occasionally in the right atrium in patients with heart failure and atrial fibrillation, and more rarely in the right ventricle in cases of massive septal infection, idiopathic cardiac hypertrophy and heart failure, or endocardial fibrosis or fibroelastosis There is some difference in reported data as to whether the greatest frequency of the thrombi is in the deep femoral veins of the thighs[54] or in the deep veins of the calf muscles[59, 26] The causative thrombi may also be situated in the iliac veins, in the superficial femoral veins the plantar veins,[61] the periprostatic veins or rarely in other veins of the abdomen, the head, neck, upper extremities or trunk Venous thrombi in the lower extremities are frequently bilateral

For a discussion of the pathogenesis of venous thrombosis see Welch[74] Hampton and Wharton[31] and Ochsner et al[4] [?] Slowing of the blood stream (venous stasis),[63, 54] injury to the vascular endothelium[60] and alterations in the physical or clinical properties of the blood which promote coagulation are the most important causative mechanisms

The pulmonary emboli themselves may block the main pulmonary artery, sometimes extending to the conus of the right ventricle and partially occluding the pulmonary valvular orifice (functional pulmonary stenosis) There may be a riding embolus at the bifurcation of the pulmonary artery But most often the emboli are multiple, occlude smaller branches of the pulmonary arteries and are of different ages[5] Pulmonary infarction does not occur when very large or very small vessels are occluded Infarction is most likely to result if a medium sized or large pulmonary arterial branch is occluded if there is preexistent pulmonary stasis and if the patient survives at least for a day or two[33, 10]

Pulmonary embolism may cause right ventricular dilatation in acute cases[44, 33] right ventricular hypertrophy in chronic cases (p 981) Myocardial necrosis of the left ventricle, especially the subendocardial regions may result from anoxia, shock or possibly pulmonary coronary reflexes which cause coronary insufficiency and myocardial ischemia[35]

PATHOLOGIC PHYSIOLOGY

There is experimental evidence that serious circulatory disturbances occur only after 60 per cent of the pulmonary circulatory cross-sectional area is cut off and that death usually follows more than 85 per cent obstruction[6, 46, 24] With lesser degrees of obstruction insufficient to cause death or reduce the systemic arterial pressures, there is an increase in pulmonary vascular resistance compensated by a stronger right ventricular contraction and a rise in right ventricular and pulmonary arterial pressure[6, 19]

Circulatory and cardiac disturbances which follow large pulmonary emboli may be due to (1) mechanical interference with cardiac output and (2) myocardial ischemia or hypoxemia The myocardial ischemia or hypoxemia may be the result of (a) a sudden and severe reduc

tion in cardiac output and aortic pressure (shock) (b) arterial hypoxemia due to pulmonary asphyxia (c) reflex vasoconstriction of the coronary arteries mediated by the vagus nerves (pulmonocoronary reflex) [61, 4, 66] or (d) impaired coronary drainage by way of the Thebesian vessels due to the rise in pressure in the right cardiac chambers [73] The possibility of a pulmonocoronary reflex has been raised particularly because of the occurrence of shock and sudden death in cases in which there were only relatively small emboli There is experimental evidence favoring[61, 69] and refuting[63, 37] this hypothesis The occasional serious consequences of small pulmonary emboli have also been explained by local reflex vasoconstriction of the uninvolved pulmonary vessels However there is considerable uncertainty as to the importance of vasomotor effects in the pulmonary vessels [14, 73]

CLINICAL FEATURES

The clinical features of pulmonary embolism are so varied and often so non specific that the diagnosis must be ventured when any of a host of possible unexplained symptoms occur in a patient in heart failure especially if he has been subjected to bed rest

1 *Shock or sudden death* with or without preceding air hunger anxiety restlessness chest pain mental symptoms ocular palsies or convulsions may be due to a sharp reduction in cardiac output

2 *Acute right ventricular strain* is usually obscured by the manifestations of diminished cardiac output but may be disclosed by electrocardiographic signs (infra) and occasionally by a prominent pulsation in the second and third interspaces to the left of the sternum accentuation of the second pulmonic sound and a loud pulmonic systolic murmur

3 *Dyspnea tachypnea* and *cyanosis* may result from impaired pulmonary ventilation and possible reflexes of undetermined nature

4 *Pulmonary and Pleural Symptoms and Signs Due to Pulmonary Infarction* These may include chest pain especially on inspiration cough bloody expectoration fever leukocytosis physical and roentgenologic signs suggesting pneumonia pulmonary neoplasm[85] or pleural effusion [73] The pleural fluid is often sanguineous The chest pain the cough and the hemoptysis may one or all be absent in many cases of pulmonary infarction Jaundice may occur in cases of pulmonary infarction and severe chronic right sided congestive heart failure

5 *Fever and Other Non specific and Unexplained Symptoms* In many or most cases of pulmonary emboli the symptoms consist only in unexplained fever often in recurrent episodes unresponsive to antibiotics and associated in cardiac patients with the development or intensification of congestive heart failure Unexplained anxiety episodes of unexplained tachycardia with or without precordial oppression anxiety or transient dyspnea or episodes of tachypnea may be the only manifestations of pulmonary embolism A paroxysm of atrial fibrillation may be initiated by pulmonary embolism Occasionally there is transient weakness faintness or syncope or an unexplained fall in blood pressure Some pulmonary emboli are virtually asymptomatic

ELECTROCARDIOGRAPHIC SIGNS OF PULMONARY EMBOLISM

In 5 of their 7 cases of acute cor pulmonale in which electrocardiograms were taken early McGinn and White[66] observed abnormalities which were fairly similar and which were interpreted as being characteristic of the condition The chief abnormalities were

1 A deep S_1

2 Prominent Q_3 and inversion of T_3 as in myocardial infarction of the posterior wall

3 Depression of ST segment in lead II and often in lead I and a staircase ascent of ST_2

4 T_2 was diphasic or inverted

5 Occasionally there was a right deviation of the electrical axis but never a left deviation during the acute episode The abnormalities disappeared in a few days

Subsequent studies have confirmed these findings with certain variations and amplifications [65, 31, 73, 47, 38, 37, 40] In particular the electrocardiographic changes observed with pulmonary embolism appear to be those associated with clockwise rotation and a vertical electrical axis as well as possible right ventricular dilatation The abnormalities are found in only 10 to 20 per cent of cases of pulmonary emboli [67] chiefly because electrocardiograms are not taken early enough or because the emboli are too small to cause a strain on the right ventricle In cases of pulmonary artery obstruction produced in the course of pneumonectomy in humans the electrocardiograms showed a shift of the

2-7-40 2-22-40

I

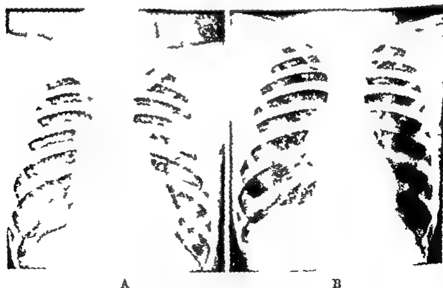
II

III

IV

A B

Fig. 145 *A* Normal electrocardiogram Left axis deviation
B S type of right bundle branch block following acute pulmonary embolism



A B

Fig. 146 *A* Pulmonary infarction left upper lobe
B Clearing of infarct with residual horizontal linear scars or focal atelectasis

electrical axis to the right and a deep S_1 in the majority of instances The changes appeared immediately and disappeared in 24 hours[8] Durant Ginsburg and Roesler[16] noted right bundle branch block with broad shallow S_1 and S_2 in the first two hours after pulmonary embolism (Fig 145) Occasionally P_2 is tall and sharp[78] Frequently the electrocardiogram of pulmonary embolism is modified by preexisting abnormalities due to myocardial disease A significant Q wave is less commonly present in aV_F in pulmonary embolism than in posterior ventricular infarction but occurs often enough to be unreliable as a distinguishing feature[56 17] A delayed R or R' may be present in aV_R S waves may be present in leads II III and aV_F

Multiple chest leads usually reveal the most persistent changes for they may not disappear for three to six weeks Wood[79] described an inversion of the T wave from V_1 to V_3 or V_4 Occasionally he observed a transient right bundle branch block (Fig 145) In addition a shift of the transitional zone to the left i e to V_4 or V_5 (clockwise rotation) has been noted in precordial leads

Clinical experimental and electrocardiographic observations strongly suggest that the electrocardiographic changes are due primarily or exclusively to acute right ventricular strain following massive pulmonary embolism[44 43 55] The possibility that myocardial anoxia is a contributing factor is suggested by the Q_3-T_3 changes resembling those of posterior wall infarction and by the pathologic findings of myocardial necrosis in cases of massive pulmonary embolism[3 15 11] However the identical electrocardiographic abnormalities have been observed in cases without myocardial necrosis

THE VECTORCARDIOGRAM IN ACUTE COR PULMONALE

A distinctive vectorcardiographic pattern has been described in cases of acute cor pulmonale and differentiated from that of posterior (diaphragmatic) ventricular infarction[37a] There was a slightly increased magnitude and duration of the initial vectors of the QRS loop There was clockwise rotation of the loop in the frontal plane and a large terminal appendage directed to the right and posteriorly occasionally superiorly The vector cardiogram of posterior infarction was distinguished chiefly by the greater increase in magnitude and duration of the superiorly directed initial vectors and by the absence of superiorly oriented terminal vectors

ROENTGENOLOGY

The roentgenologic signs directly attributed to acute cor pulmonale either are not striking or have been insufficiently studied The hilar shadows and pulmonary vascular shadows may be wider than normal The left middle salient may be prominent owing to dilatation of the pulmonary artery

Roentgenologic study[64 31 46] may suggest the presence of pulmonary infarction resulting from pulmonary embolism The shadows of pulmonary infarcts may not appear until 24 hours or several days after the occurrence of the pulmonary embolism An early sign of pulmonary infarction according to Wharton and Pierson[76] is the clouding of the base of the lung obscuring the costophrenic sinus on the affected side Infarcts are often multiple and occur chiefly in the lower lobes[67] Infarcts appear as areas of plate like atelectasis The shadows of infarcts may have the classic triangular or truncated shape (Fig 146) but more often they are round oval or irregular[31] Often they are indistinguishable from pneumonic infiltrations or from severe pulmonary congestion due to heart failure According to the studies of Hampton and Castleman[31] infarcts occur most often at the junction of two pleural surfaces and therefore the roentgen ray shadows are observed at the base of the lungs near the costophrenic sulcus at the junction of adjoining lobes and near the mediastinum (Fig 124 p 661) Pleural effusions are frequent and may conceal the shadow of the infarct itself There may be a shadow at one base with ultimate elevation of the diaphragm on that side due to partial atelectasis Rarely there is localized rarefaction indicative of necrosis or abscess Pleural thickening localized fibrosis or linear shadows may represent scars of old infarcts According to Westermark[75] and others[63] pulmonary embolism without infarction may cause transient clearing (avascularity) of the normal shadow of pulmonary tissue distal to the embolism

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of acute cor pulmonale involves (a) the diagnosis of pulmonary em

bolism plus (b) the diagnosis of right ventricular strain

Pulmonary embolism should be considered whenever there is a sudden onset of collapse, precordial oppression or chest pain, dyspnea, tachypnea or cyanosis, especially in patients who have been confined to bed for one to three weeks by cardiac disease, by an operation, fracture delivery or a medical illness Often, however, there may be only a clinical picture of shock or sudden weakness with little or no cyanosis chest pain or dyspnea Unexplained elevations in temperature and tachycardia in the second week postoperatively are often indicative of pulmonary embolism In cases of heart failure unexplained fever, lack of response to therapy or pleural effusions which are exudates or hemorrhagic should suggest the possibility of pulmonary embolism Tenderness of the calf muscles or thighs a positive Homans sign,[33] thickening and infiltration of the deep calf muscles[49] swelling of the leg or thigh and prominence of the superficial veins confirm the diagnosis Often however, there are neither symptoms nor signs of venous thrombosis In such cases venography with the aid of contrast media may disclose evidence of venous occlusion[4, 44, 16]

If death does not occur within 24 hours, the diagnosis may be further suggested or confirmed within the next few days by the development of cough and hemoptysis, localized pain on deep breathing local signs of pulmonary congestion or consolidation, a pleural rub physical signs of pleural effusion, or by roentgenologic evidences of pulmonary infarction But none of these may be present if infarction does not result from the pulmonary embolus The occurrence postoperatively or even in healthy ambulant patients[29, 33, 80] of a peculiar pneumonia or pleurisy should suggest pulmonary embolism as one of the conditions to be considered in differential diagnosis

The electrocardiogram may disclose distinctive features in about 10 to 20 per cent of pulmonary emboli but in a much higher percentage of massive emboli if the record is taken on the day of the attack (p 961)

Once a diagnosis of pulmonary embolism is made, the additional diagnosis of *acute cor pulmonale* depends on the finding of clinical evidence of pulmonary hypertension (e g, accentuation of P_2, percutory signs of a dilated pulmonary artery), roentgenologic evidence of pulmonary, right ventricular and perhaps right atrial dilatation, electrocardiographic evidence of right ventricular strain and clinical evidences of acute congestive right ventricular failure (e g, engorged cervical veins)

A problem in the differential diagnosis between coronary thrombosis and pulmonary embolism is most likely to arise when the latter is associated with chest pain The chest pain is frequently worse on inspiration in pulmonary embolism, rarely so in myocardial infarction except when complicated by early pericarditis On the other hand, the pain of myocardial infarction frequently radiates to the arms and forearms or is accompanied by weakness or numbness in the wrists unlike the pain of pulmonary embolism

The electrocardiogram of pulmonary embolism is distinguished from that of posterior ventricular infarction which it may simulate by the presence of a deep S_1 inversion of the T waves in V_1 V_2, shift of the transitional zone of QRS to the left in precordial leads and a late R in aV_R, and by the rapid reversion of these changes to normal Serial determinations of serum glutamic oxalacetic transaminase (S GOT) may aid in differentiating pulmonary embolism from myocardial infarction In many instances there is no rise in S GOT in cases of pulmonary embolism In other cases in which the S GOT is increased the level is usually not as high as in cases of acute myocardial infarction and the peak concentration occurs between the third and sixth day in pulmonary embolism, at about 24 hours after acute myocardial infarction[32a] (p 510)

PROGNOSIS OF ACUTE COR PULMONALE

The outlook after a massive pulmonary embolus is extremely unfavorable When the embolus is of sufficient size to cause shock or acute right ventricular dilatation death occurs in the majority of cases Of 100 clinical cases of pulmonary embolism reported by Takats, Beck and Fenn,[84] 87 died and 13 survived Similarly Hampton and Wharton[..] report the survival of 10 per cent of patients with pulmonary embolism following gynecologic operations Pulmonary embolism is regarded as being responsible for about 6 to 10 per cent of all postoperative deaths[3, 4, ...]

Pulmonary emboli of secondary or smaller branches are usually survived but are often of ominous significance They are frequently precursors of recurrent emboli ation which

may be terminated by a final massive embolus of the main pulmonary artery or its primary divisions In 21 4 per cent of 897 cases of pulmonary embolism studied by Barker et al [3] the first attack was fatal But of 343 fatal cases of embolism the fatal embolism was preceded by one or more non fatal emboli in 36 2 per cent These observers noted that if a patient has a non fatal postoperative pulmonary embolus he has slightly less than one chance in five of subsequent fatal pulmonary embolism and about three chances in ten of subsequent embolism fatal or non fatal The clinical signs and symptoms of small pulmonary emboli usually subside in a week or two but the clinical course may be prolonged by pleural effusion or suppuration of an infarct

Even pulmonary emboli of the primary pulmonary arteries may not cause death but may undergo organization and recanalization Such large emboli or multiple smaller emboli may occasionally produce pulmonary hypertension right ventricular hypertrophy and failure (*chronic pulmonary heart disease or chronic* cor pulmonale) (Chapter 39)

TREATMENT OF PULMONARY EMBOLISM

PROPHYLAXIS

Avoidance of Venous Thrombosis

The treatment of massive pulmonary embolism and its cardiac and circulation sequelae properly begins with prophylaxis against the development and dissemination of venous *thrombi* [I] *In medical cases it seems desirable* to avoid prolonged periods of bed rest unless *essential and to avoid immobilization of the* body *or extremities if bed rest is necessary Fortunately the dangers of bed rest especially* pulmonary embolism have recently been *publicized Since cardiac failure appears to be* a frequent predisposing cause among medical *cases adequate treatment of this condition is* important

In surgical cases care should be exercised in the handling of tissues and injury or com*pression of veins draining the lower extremities* should be avoided The position of the patient *on the operating table should cause no un*necessary interference with the venous return *Abdominal strappings or binders should not* be so tight that they prevent deep breathing *Postoperatively, abdominal distention should* be avoided or treated promptly Motion of the body should be encouraged *and regular fre*quent exercises of the legs and respiratory exercises should be ordered Adequate hydration prompt control of infection and avoidance of chilling are also believed to be valuable prophylactic measures [5] Reduction of the period of rest in bed (early ambulation not merely early sitting in a chair) may be of major importance in avoiding venous thrombosis [26] The Trendelenburg position has been recommended to avoid venous thrombosis but Frykholm[73] has opposed its use and advocated elevation of the head of the bed for one to two hours daily in order to distend the collapsed veins in the lower extremities and to compel active movements of the adductor muscles of the thigh Elastic bandages or stockings have been employed in the prophylaxis of post operative thromboembolism [71, 77]

The routine use of anticoagulants[41] has been recommended following operations injuries or other conditions requiring complete bed rest The use of anticoagulants in patients with acute myocardial *infarction* and *congestive* heart failure has been discussed (p 572 and p 287 *respectively*)

Recognition and Treatment of Venous Thrombosis

Daily examination of the legs for induration *or local tenderness over the deep veins for* pain on dorsiflexion of the foot with the leg ex*tended (Homans sign*[33]*) and for edema and* dilatation of the superficial veins and careful *measurement of the circumference of the legs* to discover swelling should be performed whenever *there is a* probability of venous thrombosis Sudden sharp chest pain *faintness hemoptysis fever tachycardia dyspnea or other manifestations of pulmonary em*bolism are usually the first indications of an underlying phlebothrombosis which is then discovered by *local examination*

The treatment of venous thrombosis (phlebothrombosis) to avoid initial or recurrent pulmonary embolism consists essentially of two measures (1) anticoagulant therapy or (2) thrombectomy and venous ligation

Although there has been a strong trend in favor of anticoagulants in the treatment (as well as prevention) of venous thrombosis and as a prophylaxis against pulmonary embolism venous ligation still has its adherents [72, 1, 7] In a recent review of 748 cases of phlebitis Byrne[7] reported a mortality rate of 2 1 per

cent in 369 cases treated by bilateral femoral vein ligation or occasionally by division of the inferior vena cava, a mortality rate of 29 per cent in 32 cases treated by anticoagulants, and a mortality rate of 37 per cent among 347 cases treated conservatively However, the mortality rates may have been determined by the basic disease rather than by the method of treatment

The details of anticoagulant therapy have been discussed (p 572) The ligation of the inferior vena cava for intractable heart failure has been mentioned (p 290)

TREATMENT OF PULMONARY EMBOLUS

The direct treatment of the pulmonary embolus itself aside from the use of anti coagulants is unsatisfactory Based on the *experimental observations which indicate the* occurrence of vagal reflexes with spasm of the coronary vessels and other smooth muscle structures *atropine* has been administered *intravenously* in repeated doses of 0 6 mg (1/100 grain), and *papaverine hydrochloride* by the same route in doses of 0 03 gm (½ grain) With massive embolization the latter may be repeated at hourly intervals Morphine or Demerol may be necessary for pain and restlessness

Oxygen should be administered in cases of massive pulmonary embolism by nasal catheter, mask or tent or in 100 per cent concentration by the special mask of Boothby and his associates [6]

Surgical removal of an embolus in the main pulmonary artery or its bifurcation (Trendelenburg operation) has been successfully performed and strongly advocated by Kirschner[19] and Meyer [11] This requires a well trained organization which may be rapidly set into action when the diagnosis is made The procedure can be utilized *for those patients who* survive more than an hour According to de Takats, Beck and Fenn,[69] the Trendelenburg operation was carried out 132 times with a mortality of 93 2 per cent, but these operations were performed almost exclusively on rapidly fatal cases

FAT EMBOLISM

Embolism of the pulmonary circulation may result from the entrance of free globules of fat into the systemic veins [31, 79] Fat embolism *occurs most commonly* after a fracture of a long bone especially the femur, tibia or both [9, 91] But it may occur also after other forms of trauma to bone marrow or subcutaneous adipose tissue osteomyelitis, various poisons or burns [90]

The released fat enters the systemic veins and may reach and obstruct the main pulmonary artery,[87] thus sharply reducing the cardiac output and causing acute cor pulmonale More frequently the fat globules reach the *pulmonary capillaries, where they may be* trapped and where they may cause widespread pulmonary obstruction with lesions in the affected lung tissue As a rule some of the globules of fat traverse the pulmonary capillaries and reach the systemic (arterial) circulation, where they block the capillaries and arterioles of the brain, the skin, heart and numerous internal organs Fat emboli may *also reach the systemic* circulation from the right side of the heart by way of a patent foramen ovale The occurrence of clinically significant coronary occlusion due to fat embolism is unproven [11]

The *clinical features* are determined chiefly by embolic lesions in the lungs and the brain *Characteristically, after an injury* the patient has a free interval of relative comfort lasting from six hours to two or three days If there is a massive occlusion of the pulmonary artery by a large quantity of liquid fat, death may occur suddenly with a clinical picture of shock air hunger and pulmonary edema *More commonly, a few days after* the injury the patient begins to suffer from dyspnea and restlessness followed by sweating pallor or cyanosis, and cough with blood tinged sputum These manifestations are due to occlusion of the pulmonary *capillaries by fat* Tachycardia tachypnea and fever are frequent There are often *diffuse moist* râles and other signs resembling those of pulmonary *consolidation* or edema Shock and pulmonary edema occur in severe cases [89] Free fat droplets may be demonstrated occasionally in the sputum by staining with Sudan III, *but it is* doubtful whether this is pathognomonic of pulmonary fat embolism *Roentgenograms* of the chest may reveal bilateral patchy pneu*monic consolidation* or pulmonary edema

Cerebral symptoms may be combined with or follow these pulmonary manifestations They should not be misinterpreted *in cases of* head injury, and must be differentiated from cerebral manifestations of concussion and cerebral hemorrhage shock, delirium tremens,

uremia diabetic coma and bronchopneumonia ■ More often they appear several hours to days after the injury without preceding pulmonary symptoms The patient suffers from somnolence disorientation or delirium There may be convulsions paralyses loss of sphincteric control and stertorous or Cheyne Stokes respiration Fat emboli in the retinal arteries have been visualized opthalmoscopically ■ Occasionally fever stupor and coma are the essential signs of fat embolism without preliminary pulmonary or localizing cerebral signs The occurrence of dark red petechial hemorrhages on the skin of the anterior chest, arms neck conjunctivae and mucous membranes is of diagnostic value

Recovery may occur,[93] probably independently of the treatment employed In fatal cases death usually occurs after two or three days The avoidance of further trauma in handling and transporting injured patients is emphasized in the prophylaxis of fat embolism Treatment is symptomatic Oxygen therapy is administered if there is cyanosis and dyspnea Norepinephrine has been recommended Sodium desoxycholate (10 cc of 20 per cent solution by slow intravenous drip every two hours) has been suggested as a therapeutic measure by Rappert ■ with the object of emulsifying the fat globules and thus reducing the elevated blood viscosity

AIR EMBOLISM

Systemic Venous (Pulmonary Arterial) Air Embolism

When air rapidly enters the systemic veins in large quantities it reaches the right ventricle where because of its easy compressibility it acts as an air trap and interferes with ventricular contraction Air embolism may obstruct the main stem of the pulmonary artery [103] causing pulmonary hypertension with reflex systemic hypotension and bradycardia [100] It may also produce pulmonary obstruction by causing widespread embolization of the pulmonary arterioles or capillaries [101] An average lethal dose is 5 to 7 5 cc per kilogram when the rate of intravenous injection is very rapid (1 to 5 seconds) According to Curtillet [94] air bubbles do not reach vessels less than 30 micra in diameter and therefore they are arrested in the arterioles The presence of air in the ventricular cavity may be revealed by a loud churning or waterwheel murmur over the precordium Death often results suddenly with or without premonitory cyanosis or pallor, evidences of shock, dyspnea and stertorous respiration and coma These manifestations result from diminished cardiac output pulmonary hypoxemia and eventually cerebral hypoxemia [94]

Systemic venous air embolism occurs mostly in the course of major surgical operations on the thyroid gland and other structures of the neck where the veins are large and kept widely patent by fascial structure but it may also complicate numerous minor diagnostic and therapeutic procedures These include among others tubal insufflation and urethroscopy perirenal insufflation, irrigation of the nasal sinuses pneumoperitoneum direct transfusions, and uterine douches or adoption of the knee-chest position in the puerperium Air embolism has been noted after criminal abortions and vaginal powder insufflations [99]

Prompt treatment is important In the experimental animal with systemic venous emboli (to the right ventricle) displacement of the air trap by turning the body into the left lateral position may be lifesaving ■ Therefore it ■ recommended that following venous air embolism the patient should be placed in the left lateral position (right side up) and given artificial respiration [96, 100] If these measures are ineffective a needle should be inserted through the chest wall into the right ventricle in an effort to aspirate air Inhalation of 100 per cent oxygen has been recommended on the basis of experimental studies [97]

Arterial Air Embolism (Pulmonary Venous Air Embolism)

According to experimental studies smaller quantities of air are required to cause death when injected into a pulmonic vein than when injected into ■ systemic vein [100] When air enters the pulmonary vein it reaches the left side of the heart and systemic arterial circulation Such arterial air emboli may also occur when air ■ introduced into a systemic vein if there is an interatrial communication As a rule air emboli reaching the pulmonary arterioles from a systemic vein do not cross to the pulmonary vein and systemic arterial circulation as do fat emboli [94] Arterial air emboli cause serious symptoms chiefly by occluding arterioles or capillaries of the brain Air emboli also involve the coronary arteries at the same time [100] Durant[95] reported a case of air embolism in which there were characteristic electrocardiographic changes such as occur

after a cardiac infarction By means of roentgenography Balogh[93] noted a reflux of air from the right ventricle into the thebesian and coronary veins He believed that this causes coronary stasis and may be responsible for clinical symptoms

Clinically *systemic arterial air embolism* results most often from the entrance of air into the pulmonic veins in the course of pleuropulmonary operations or artificial pneumothorax [98, 80] It also occurs after chest injuries and pleural lavage of empyema cavities So-called pleural shock may in reality represent air embolism Symptoms appear rapidly, beginning with dizziness or pallor and followed by mental confusion disorientation hallucinations convulsions vomiting paralyses, especially hemiplegia or monoplegia, aphasia and amaurosis The latter is due to air embolism of the retinal arteries which sometimes may be visualized clinically with the ophthalmoscope [102] Marbling of the skin may result from obstruction of the cutaneous vessels or from shock Coma and death may occur within fifteen minutes Patients surviving an hour or longer usually recover Blindness and paralyses disappear in most cases but there may be residua

Therapy is unsatisfactory Maintenance or assumption of the head-down position is recommended to avoid floating of the air bubbles into the cerebral vessels The Trendelenburg position is desirable at operations in which air embolism may be anticipated (e g chronic pulmonary abscess)

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Chapter 39

CHRONIC PULMONARY HEART DISEASE—COR PULMONALE

Definitions

Pulmonary heart disease and *cor pulmonale* are terms applied to the hypertrophy of the right ventricle with or without congestive heart failure, resulting from disease of the lungs or pulmonary vascular tree Pulmonary heart disease is often divided into the *acute form* induced by massive pulmonary embolism the *subacute form* due to lymphangitic carcinomatosis of the lung and the *chronic form* due to obstructive emphysema or other chronic pulmonary disease Cor pulmonale was often called *emphysema heart* because emphysema is the commonest cause of pulmonary heart disease

Ayerza's Disease or Syndrome The term Ayerza's disease[129] or Ayerza's syndrome refers to a clinical syndrome characterized by bronchopulmonary disease, intense cyanosis polycythemia and congestive heart failure, usually associated with bronchopulmonary symptoms but without primary cardiac disease Ayerza had referred to the syndrome as *cardiacos negros* (black cardiacs),[7] because of the deep cyanosis of the affected patients At present there are multiple concepts of the etiology of Ayerza's syndrome even among Ayerza's students One theory attributes it to syphilitic pulmonary arteritis,[4, 46] another to bronchial syphilis and pulmonary arteriosclerosis[47] another to primary non syphilitic sclerosis of the pulmonary artery and still another to various bronchopulmonary diseases with or without secondary pulmonary atherosclerosis[35] Ayerza's syndrome is not synonymous with cor pulmonale but represents a clinical syndrome at one stage of cor pulmonale when there is advanced pulmonary insufficiency as well as decompensated cor pulmonale

Hypertension of the Pulmonary Circulation

Despite a varied etiology of chronic cor pulmonale, it is generally assumed that there is probably a unitary mechanism producing it namely, an increased resistance and therefore an increased pressure in the pulmonary circuit Measurements of the right ventricular pressure by intracardiac catheterization have disclosed an elevation of the systolic and pulse pressures, but the diastolic ventricular pressure was normal in the absence of heart failure[27] The occurrence of exclusive or predominant right ventricular hypertrophy is an direct evidence of increased pulmonary resistance to ventricular outflow The increased frequency and extent of pulmonary atherosclerosis in cases of chronic cor pulmonale has also been interpreted as resulting from and denoting the presence of pulmonary hypertension[132, 157]

Pulmonary Hypertension and Chronic Cor Pulmonale

Pulmonary hypertension may be caused by a variety of pulmonary, cardiac and vascular disturbances which fall into three broad groups

1 Mitral stenosis and less commonly other causes of left sided heart failure which result in pulmonary congestion

2 Extensive disease of the lungs or pulmonary arteries which greatly increases the resistance in the pulmonary circulation Obstruction of the pulmonary artery from without by a compressing aortic aneurysm or tumor may produce a similar effect[91]

3 Congenital cardiac lesions such as large and high ventricular septal defects and patent ductus arteriosus with reversal of shunt are associated with pulmonary hypertension In some instances of congenital heart disease pulmonary hypertension is due to pulmonary arterial lesions Such cases properly belong to group 2

The term chronic cor pulmonale or chronic pulmonary heart disease as used in this chap-

ter and elsewhere in this book is confined only to the second group in which pulmonary hypertension and consequent strain of the right heart are caused by primary disease of the lungs or pulmonary vessels But pulmonary hypertension due to any of the above causes may induce right ventricular hypertrophy and right heart failure

PULMONARY FUNCTION TESTS AND LUNG VOLUMES

The pulmonary lesions which are responsible for pulmonary hypertension and cor pulmonale also cause disturbances in pulmonary ventilation and aeration of the blood Consequently the physiologic disturbances and clinical manifestations of cor pulmonale are accompanied by disturbances in pulmonary ventilation and aeration An understanding of cor pulmonale therefore requires a knowledge also of pulmonary function and of the disturbances due to abnormalities in pulmonary ventilation and aeration

The ultimate function of the lung is to aerate the venous blood by supplying it with oxygen and removing carbon dioxide This involves three subsidiary functions (1) ventilation whereby air is moved into and outside of the lungs and well distributed to the pulmonary alveoli which are in contact with the pulmonary capillaries (2) alveolar capillary diffusion whereby alveolar oxygen diffuses into the capillaries and capillary carbon dioxide into the alveoli (3) circulatory or alveolar perfusion whereby the entire circulation passes through the pulmonary capillary bed Cor pulmonale is due chiefly or exclusively to the effect of intrinsic pulmonary disease on the pulmonary vascular bed However, impaired ventilation or alveolar-capillary diffusion may cause disturbances which indirectly alter the pulmonary circulation and add to the strain on the right ventricle In addition the disturbances in ventilation and aeration produce symptoms which resemble those of heart failure and must be distinguished from them

Tests of pulmonary function determine individual features such as the air capacity of the lungs the dynamic ability to move air into and out of the bronchial passages (bellows function) the ability to distribute air fairly uniformly to the perfused alveoli and the ability to diffuse oxygen and carbon dioxide across the alveolar-capillary membrane The over all function of the lung is assessed by determinations of the oxygen and carbon dioxide tensions and of the pH of the arterial blood and by the work or effort involved in breathing

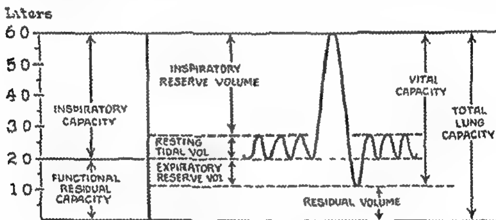


Fig 147 Subdivisions of total lung capacity

Lung Volumes (Fig 147)

The lung volumes denote the volumes of air that can be inhaled or exhaled from specific inspiratory or expiratory positions The lung volumes are conventionally measured from the so-called pulmonary mid position i e at the end of a quiet expiration Except for the residual air the various lung volumes may be measured by a spirometer preferably a recording spirometer of the closed circuit type e g, the Collins spirometer similar to the Benedict-Roth apparatus used for basal metabolism tests However the spirometer bell is larger measuring about 9 liters in capacity

and is filled with room air The tubing is of larger caliber (about 1½ inches inside diameter) and the soda lime container and flutter valves of the basal metabolism machine are removed to reduce resistance

Tidal Air The tidal air is the quantity of air inhaled and exhaled from the lungs during an ordinary respiration and amounts to about 500 cc After a quiet exhalation followed by an *ordinary inspiration an ordinary exhalation* is made into the spirometer and this quantity of exhaled air is measured as the tidal air

Inspiratory Capacity (Complemental Air) This is the maximum volume of air that can be inhaled from the resting pulmonary mid position While connected to the spirometer the subject takes a few normal breaths and then is directed at the end of a quiet expiration to inhale as deeply as possible The inspiratory capacity includes the tidal air and the inspiratory reserve which together equal about 3 liters normally

Inspiratory Reserve The amount of air which can be further inhaled at the end of an ordinary inspiration is the inspiratory reserve, which normally amounts to about 2500 cc

Expiratory Reserve Volume (Reserve Air or Supplemental Air) This is the maximum volume of air exhaled after a quiet expiration that is *from the pulmonary mid position* At the end of a quiet expiration, and without subsequent inspiration the subject exhales as much air as possible into a spirometer thus recording the reserve air Normally it is about 1000 cc

Vital Capacity (V C) The vital capacity is the maximum volume of air that can be exhaled following a maximum inspiration It includes the inspiratory capacity and the expiratory reserve The inspiratory capacity is 75 to 80 per cent *of the vital capacity and* the expiratory reserve 20 to 25 per cent Following a maximum inspiration the patient exhales as completely as possible into a spirometer thus measuring the vital capacity Normally the vital capacity is about 4 or 5 liters, with considerable variation Normal values may be calculated roughly by West s formula for males V C (liters) = 2 5 times body surface area in sq meters for females, V C = 2 times body surface area Or more accurately, by the regression formula of Baldwin et al [10] for males [27 63 − (0 112 × age in yrs)] × ht in cm , for females, [21 78 − (0 101 × age)] × ht

Residual Volume The volume of air remaining in the lung after a maximal expiration is the residual volume This air remains in the alveolar air sacs because the negative intra thoracic pressure prevents their collapse The normal residual volume is approximately 1500 cc

Total Lung Volume or Capacity This equals the sum of the vital capacity and the residual air, and *represents the total volume of air in* the lungs at maximal inspiration

Functional Residual Capacity and Residual Air (Residual Capacity) The *functional residual* capacity is the volume of air in the lungs at the end of a quiet expiration It is the sum of the expiratory reserve and the residual volume Neither the residual volume nor the functional residual capacity can be measured by direct spirometry The expiratory reserve is measured by spirometry as indicated above The functional residual capacity may be measured indirectly by the open circuit or closed circuit method (infra) The residual volume (residual air) is then determined by subtracting the expiratory reserve from the functional residual capacity

To determine the functional residual capacity by the *open circuit* method,[12, 67, 46, 11] a Tissot spirometer and tubing are washed free *of nitrogen by means* of 100 per cent oxygen and the subject then quietly breathes oxygen for 7 minutes Douglas bags instead of the Tissot *spirometer may be used for* collections of air from the lungs An alveolar sample is obtained at the end of that period by taking the sample of air at the very *end of a maximal* expiration After the volume of the air expired into the spirometer is measured, the nitrogen concentration of the expired air in *the spirom* eter and that of the alveolar sample are *determined* with the Van Slyke manometric apparatus The functional residual *air* can be calculated from a formula which essentially consists in dividing the amount of nitrogen expired by the reduction in alveolar nitrogen concentration during the period of oxygen breathing An open circuit method using helium has also been described [109, 24]

A number of methods have been devised using the closed circuit technique [43, 115, 41] The subject breathes into a closed circuit, including a spirometer containing known volumes and concentrations of oxygen,[4] hydrogen[147] or helium [83, 152] Or the nitrogen may be washed out of the lung by breathing oxygen and the

concentration of nitrogen can be serially determined with the aid of a nitrogen meter[78] Thus the need for obtaining alveolar samples can be obviated After a few breaths or several minutes of breathing it is assumed that there is complete mixing of the gases in the spirometer and lungs A katharometer which measures changing conductivity of a gas may be used to indicate completion of mixing in the circuit and lungs The functional residual volume is calculated from the known initial and final volume and the concentration of the gas in the spirometer In modern machines such as the Collins Vitalometer the helium volume introduced and the final concentration of helium are read directly from the kymographic record and a helium meter With the same spirometer the inspiratory capacity and expiratory reserve are measured and the individual lung volumes calculated

Kovack et al[1-8] described a method whereby the total lung capacity was calculated from various measurements made from a single posteroanterior film of the chest taken in deep inspiration The residual air is then determined by subtracting the vital capacity from the total lung capacity Du Bois et al[678] described a new plethysmographic method for measuring the resting end-expiratory thoracic gas volume i e the functional residual capacity There was excellent agreement with measurement by the open circuit method

Respiratory Dead Space The *anatomic dead space* refers to those parts of the respiratory system which serve primarily as conducting airways (mouth nose pharynx larynx trachea bronchi and bronchioles) and within which there is no rapid exchange of oxygen and carbon dioxide The *physiologic dead space* includes the areas of the lung (alveoli) which are ventilated but not perfused by blood and which therefore do not contribute to the exchange of oxygen and carbon dioxide The combined respiratory dead space is about one quarter of the tidal volume and should not exceed one third of the latter In certain pulmonary diseases notably emphysema there is no significant change in the anatomic dead space but the physiologic dead space is increased because of the underperfusion or lack of blood perfusion of ventilated alveoli[224] Air leaving these alveoli is virtually unchanged inspired air The dead space effect (D S) may be stated as a percentage of tidal air (or of total ventilation) and may be estimated as follows

$$DS = \frac{\text{arterial } pCO_2 - \text{Expired } pCO_2}{\text{arterial } pCO}$$

The respiratory dead space can be measured by a single breath analysis of carbon dioxide oxygen nitrogen or helium by use of the mass spectrometer and simultaneously with a Lilly nitrogen meter[17 35]

Significance of Lung Volumes The absolute values of the various lung volumes are of relatively limited value as tests of pulmonary function Comparative serial measurements of the vital capacity in contrast with absolute values may be useful in following changes in cardiopulmonary function In general only gross deviation from the predicted value of the various lung functions is of significance A reduction in vital capacity occurs with a reduction in the amount of aerated lung parenchyma (restrictive ventilatory insufficiency) and may or may not be altered with the more serious obstructive disturbances of the bronchial airways as in pulmonary emphysema In restrictive pulmonary disease both the inspiratory capacity and expiratory reserve components of the vital capacity are diminished and eventually the expiratory reserve may virtually disappear An increased expiratory reserve may denote hyperinflation due to obstruction but without loss of pulmonary elasticity since the lungs can be normally deflated

Ratio of the Residual Capacity to the Total Capacity Normally this ratio which has been found of greater significance than individual static lung volumes varies between 20 and 35 per cent and should not exceed 40 per cent Occasionally it is higher in apparently normal individuals beyond the age of 50 *It is notably* increased in obstructive pulmonary emphysema and amounts to 40 to 45 per cent in moderately severe cases 45 to 55 per cent in severe cases and more than 55 per cent in very severe cases

Dynamic Pulmonary Function Tests

Various dynamic pulmonary function tests have been devised in an effort to determine the speed and efficiency of pulmonary ventilation as well as the relatively static lung volumes The following are among those most commonly employed

Timed Vital Capacity The vital capacity is measured by a spirometer with an attached

timing device which permits measurements of the fractions of the total vital capacity moved in the first second and third seconds of the test [87, 160] The normal person exhales virtually 100 per cent of the total capacity in the first 3 seconds about 95 per cent in the first 2 seconds and about 80 to 85 per cent in the first second When smaller fractions of the vital capacity are registered during these intervals, there is a ventilatory defect which is primarily due to increased resistance to airflow or loss of pulmonary elastic tissue

Maximal Breathing Capacity [95] The subject breathes in and out of a spirometer as deeply and as rapidly as possible for about 15 to 30 seconds The resulting volume is converted into liters per minute The subject must be urged on to increased effort during the procedure The patient breathes with the aid of a mask or mouthpiece through tubing of large internal diameter and with low resistance valves into a Tissot spirometer a Douglas bag or a modified gas meter [10, 11, 237]

The average normal values of maximal breathing capacity for women vary between 60 and 125 and for men between 70 and 175 liters per minute The following formulas have been used to predict maximal breathing capacity (M B C)

Males M B C =
[86 5 − (0 522 × age in yrs)]
× sq meters body surface area

Females M B C =
[71 3 − (0 474 × age in yrs)]
× sq meters body surface area [10]

There is no constant relationship between the maximal breathing capacity and the vital capacity in patients with pulmonary disease [45] In cases of obstructive emphysema small reductions in vital capacity may be associated with marked diminution in maximal breathing capacity The maximal breathing capacity depends on the ability to move air in and out of the lung *rapidly* and is most likely to be diminished when there is increased resistance to airflow due to bronchial narrowing or obstruction

The relation of maximal breathing capacity to vital capacity is sometimes expressed in terms of the *air velocity index*,[88] which is the per cent of actual as related to predicted M B C divided by the per cent of actual as related to predicted vital capacity Normally this index is 0 9 to 1 2 Low indexes suggest the presence of bronchial obstruction

The *ventilatory reserve* is the difference between the actual minute ventilation at rest and the maximal breathing capacity [11] It is often expressed as a percentage of the maximal breathing capacity and is regarded as a measure of ventilatory efficiency Normally it is 85 per cent or more Dyspnea is usually present when the ventilatory reserve is less than 70 per cent of the maximal breathing capacity [10]

The *minute ventilation* or minute volume of natural respiration is determined by multiplying the tidal volume by the rate of respiration, or it is determined directly by the use of flow meters which register the volume respired over a given period of time When the minute volume is to be obtained during exercise it is preferable to collect the expired air into a Douglas bag or flow meter rather than into a Tissot spirometer

The *ventilation equivalent* is the volume of air which is ventilated while the subject absorbs 100 cc of oxygen This is normally between 2 and 3 liters This may also be expressed in terms of oxygen absorbed per liter of ventilation normally 40 to 50 cc per liter

Respiratory Pattern

The pattern of respiration recorded with various spirometers or with a pneumotachograph may be significant in the diagnosis of various types of pulmonary disease In the normal individual, rapid unimpeded flow of air in and out of the chest is shown by the almost perpendicular slope of the inspiratory and expiratory tracing The tracings return to the same resting position with successive performances When there is obstruction and slowing of the air flow in and out of the chest the steepness of the slope of the spirographic tracing is diminished In obstructive emphysema the patient is unable, on successive measurements of vital capacity, to return to the same resting level This is evidence of air trapping or of changes in lung elasticity Trapping is also indicated by sharp reduction in vital capacity when successive determinations are made without pause

Alveolar Distribution of Inhaled Air Index of Intrapulmonary Mixing

In certain pulmonary diseases, notably pulmonary emphysema, alveolar ventilation is often imperfect and uneven, and some over ventilated alveoli are poorly perfused with blood whereas other alveoli are perfused with

blood but inadequately ventilated A test or index of intrapulmonary mixing is obtained by having the subject breathe pure oxygen for seven minutes[45] The thoroughness of mixing is determined by the completeness with which the inert gas nitrogen has been washed out of the alveoli In normal persons the nitrogen concentration in an alveolar sample after oxygen breathing is less than 2 5 per cent In patients with emphysema the index may range from 4 to 15 per cent

Alveolar Blood Diffusion

The above tests are essentially measures of the bellows function of the lungs i e the ability to bring oxygen to the alveoli and remove carbon dioxide This represents pulmonary ventilation in the narrower sense In addition performance of the over all function of the lungs requires that the alveolar oxygen be diffused into the pulmonary capillary blood and the carbon dioxide removed therefrom The rate of diffusion of oxygen or carbon dioxide across the alveolar capillary membrane is proportional to the specific diffusion constant of that gas and the difference in tensions of the gas (in millimeters of mercury) on either side of the membrane The alveolar carbon dioxide tension is virtually identical with carbon dioxide tension in pulmonary capillary blood (about 38 to 40 mm Hg) the capillary tension being higher by about 0 5 mm Hg[74] The alveolar partial pressure of oxygen is 1 to 2 mm Hg higher than the pulmonary capillary oxygen tension the difference representing a slight alveolar-capillary oxygen gradient But because of the venous admixture the oxygen tension in the arterial blood is about 5 to 10 mm Hg lower than the partial pressure of oxygen in the alveoli[1, 9, 74, 71] (95 mm Hg in the former 100 to 105 mm Hg in the latter) When this alveolar arterial (A a) oxygen gradient is increased it is important to know whether the increase is caused by augmented venous admixture (e g due to poor or uneven alveolar ventilation) or to impaired alveolar capillary diffusion

Accurate determinations of alveolar and pulmonary capillary oxygen concentrations are difficult because direct samples of alveolar air or pulmonary capillary blood cannot be obtained Alveolar air is now obtained by continuous end-expiratory sampling or its composition is calculated from the inspired oxygen tension respiratory quotient and the arterial carbon dioxide tension the last of which is regarded as identical with alveolar carbon dioxide tension[184, 71] Arterial blood is used instead of pulmonary capillary blood to determine oxygen tension Arterial oxygen and carbon dioxide tensions are determined by equilibrating arterial blood in a tonometer with gas of known tension[152]

Differentiation of an increased alveolar arterial (A a) oxygen tension difference due to venous admixture from that due to impaired alveolar capillary diffusion (pulmonary membrane factor) is accomplished by determining the A a difference at two levels of oxygen intake e g when breathing room air and when breathing 14 per cent oxygen[1, 9, 183] Analysis of the alveolar arterial oxygen tension (P_{O_2}) gradient under these two conditions permits the estimation of the mean alveolar-capillary P_{O_2} difference which is divided into the oxygen uptake to give the diffusing capacity for oxygen (D_{O_2}) Other methods using carbon monoxide breathing have also been utilized to estimate the diffusing capacity of the lungs[74] Owing to the character of the oxygen dissociation curve venous admixture is the dominant factor determining the A a oxygen difference when the patient breathes ambient air at sea level pressures whereas the membrane component is predominant when the subject breathes lower concentrations of oxygen i e oxygen at low partial pressure In certain diseases characterized by extensive pulmonary fibrosis disturbances in aeration of the blood are due essentially to impaired alveolar-capillary diffusion (alveolar-capillary block)[9]

Work of Breathing and Respiratory Effort

From the clinical viewpoint pulmonary disease leading to significant ventilatory disturbance is important because it produces symptoms notably dyspnea In recent years dyspnea has been related to the increased work of breathing or the respiratory effort imposed on the muscles of respiration by the disturbances in ventilation This work is represented by the changes in lung volumes effected against various resistances elastic recoil or *elastance* of the lung airway resistance and frictional and other tissue resistance (viscance) The force or effort exerted is indicated by the pressure difference between that at the airway opening or mouth (atmospheric pressure) and that at the surface of the

lungs or pleura (intrapleural pressure) The rate at which the work is performed is likewise important

Measurement of Work of Breathing The work of breathing may be estimated indirectly by the oxygen utilization during quiet breathing and during hyperventilation Pulmonary disease may be associated with a high resting oxygen consumption, owing to the excessive oxygen requirement of respiration itself and with excessive oxygen consumption during hyperventilation [59]

Direct determinations of the mechanical work of respiration involve the measurement of (1) the transpulmonary pressure (mouth intrapleural pressure difference) (2) the volume of gas displaced (respiratory volume) and (3) the rate of volume displacement (rate of flow) [60] Intra esophageal pressure, measured by an intra esophageal balloon, mirrors intrapleural pressure and may be used in place of the latter, thus obviating the need for a thoracentesis [59, 86] Rates of air flow are recorded with a pneumotachograph connected to a manometer Direct measurement of volume changes is effected by electrical integration of the rate of flow curve, eliminating the need for tedious planimetry Direct plotting of the pressure flow curves is accomplished by simultaneous recording of the flow rates, volumes and pressures in a direct writing cathode ray oscillograph

Measurement of Viscoelastic Properties of Lung From the recorded loops one can determine the volume change per unit of elastic pressure change The *compliance* or distensibility of the lung is measured as the

$$\frac{\text{volume change (liter)}}{\text{pressure change (cm water)}}$$

The greater the volume change per unit of pressure change the greater the compliance of the lung and the less the *elastance* Elastance is the inverse of compliance [209, 150, 85, 81] The term elasticity of the lung as commonly used or misused, denotes pulmonary *compliance* or distensibility But according to physicists "elasticity" denotes the resistance to deformation the opposite of distensibility and this elastic resistance of the lung is now termed elastance A rigid lung has more than normal elastance, less than normal compliance Normal compliance is about 0 22 liter per centimeter of water pressure The determination of pulmonary elastic resistance (elastance) independent of airflow and frictional and other tissue resistance is determined by measurements at the moments when respiratory airflow ceases e g , at the end of inspiration

The frictional forces involved in pulmonary respiration are expressed as *resistance* or viscous work and are measured as

$$\frac{\text{pressure change (cm water)}}{\text{air flow (liters per sec)}}$$

The compliance and the resistance (frictional forces) are referred to as the *viscoelastic properties* of the lung The flow resistance component of the total transpulmonary pressure is determined by electrical subtraction of the component due to elastic resistance from the total pressure difference Normally the airway resistance is about 1 7 cm water per liter per second of airflow The normal respiratory work varies from 0 3 kg m per minute with quiet breathing to a maximum of 80 kg m per minute with maximal hyperventilation [14] A new method for measuring airflow resistance by means of a body plethysmograph has been described [a b]

In cases of severe pulmonary emphysema an increase of work of breathing has been observed which is related chiefly to airflow resistance and to a much lesser extent to elastic resistance (elastance) of the lung [144, 149] Airflow resistance is increased during expiration and especially with increased frequency and effort of respiration [41] Pulmonary compliance is relatively normal during quiet breathing, but increases with increased breathing frequency [149] Increased work of respiration has also been measured in cases of mitral stenosis especially with heart failure, and this is due chiefly to increased elastance or rigidity i e to diminished pulmonary compliance [1 7]

With quiet respiration at slow rates most of the work of breathing is performed against the elastic resistance (elastance) whereas with increased rate of respiration and less pulmonary distention more work is performed against airflow and tissue frictional resistance It has been noted that there is an optimal rate of breathing at which the necessary ventilation is accomplished by minimal work and that normal subjects at rest and during exercise breathe at that respiratory rate which is most economical in terms of work of respiration [146] This may be of interest in connection with the observation that breathing is relatively shallow and rapid in patients with left sided heart failure and pulmonary fibrosis, in which there is increased elastance with rela

tively little airflow resistance and low in patients with emphysema in which the increased resistance is due chiefly to the airflow component For airflow resistance predominates and is chiefly intensified by rapid respiration whereas elastic resistance predominates with deep respiration at low rates

Dyspnea and Inspiratory Force Recent studies have related the occurrence of dyspnea not to the *work* of breathing but to the *inspiratory force* exerted on the lungs as reflected by the negative intrapleural pressure during inspiration.[111] Each subject was found to have a limiting force exerted on the lungs at which threshhold further respiratory effort was prevented by dyspnea or occasionally by fatigue Normal individuals and patients with mitral stenosis or pulmonary emphysema may be exerting the same respiratory force at their limit of respiratory effort but at this limit normal individuals are ventilating 100 to 120 liters per minute whereas patients with mitral stenosis or emphysema are only ventilating 30 to 40 liters per minute In order to satisfy the respiratory stimulus occasioned by mild or moderate exercise the normal individual may accomplish adequate ventilation with less than this maximal inspiratory force whereas patients with mitral stenosis or emphysema must exert this maximal inspiratory force which induces dyspnea The capacity to increase respiratory work is limited also by the resistance to distention of the lung and airflow and by the maximum rate which will permit economical work of respiration.

Arterial Gases and pH Pulmonary (Respiratory) Insufficiency

Determination of the arterial oxygen saturation and tension, of the carbon dioxide content and tension and of the pH discloses whether the ultimate function of the lung namely aeration of the blood is being properly carried out The methods have been discussed (p 226) [79] Normal arterial oxygen saturation is 95 to 98 per cent and the more significant normal oxygen tension is about 95 mm Hg The arterial carbon dioxide content is 50 volumes per cent (22 millimols per liter) and the arterial carbon dioxide tension 40 mm Hg

Disturbances in ventilation or in alveolar capillary diffusion may occur but aeration of the blood (oxygenation and removal of carbon dioxide) may be normal as a result of compensatory increase in the rate force or work of breathing Thus there may be ventilatory or diffusion insufficiency without over-all pulmonary insufficiency When the carbon dioxide tension rises or the oxygen tension of arterial blood falls as a result of pulmonary disturbance *pulmonary insufficiency* is present as well as insufficiency of ventilation or diffusion. Cyanosis is the characteristic sign of pulmonary insufficiency as dyspnea and hyperventilation are the manifestations of ventilatory insufficiency But cyanosis may not be visible with minor degrees of arterial hypoxemia and increased arterial carbon dioxide content and diminished oxygen may contribute to causing dyspnea. It should be recalled that because of the nature of the oxyhemoglobin dissociation curve minor reductions in oxygen saturation may denote a significant diminution in oxygen tension (Fig 56 p. 229)

The *effect of exercise* in tests of ventilatory and diffusion function and in over all pulmonary function is of utmost importance as it is in determining cardiac function. Many of the tests thus far described are performed with the patient at rest and undergoing exercise Walking step tests foot-pedaling and raising weights and voluntary hyperventilation are some of the stresses employed

The arterial oxygen and carbon dioxide determinations are often normal in patients with pulmonary disease at rest but oxygen tension falls and carbon dioxide tension may rise with exercise [22] Pulmonary insufficiency thus appears only with exertion. Because of the much greater diffusibility of carbon dioxide than oxygen carbon dioxide concentrations are often normal in patients with arterial hypoxemia due to pulmonary disease In diseases associated with hyperventilation (pulmonary fibrosis pulmonary congestion in left-sided heart failure) the hyperventilation may actually reduce arterial carbon dioxide (hypocapnia) Eventually in extensive pulmonary disease with obstructive emphysema impaired ventilation and alveolar aeration result in the accumulation of carbon dioxide in arterial blood (hypercapnia) Hypercapnia representing gaseous acidosis is distinguished from that denoting metabolic alkalosis by determination of arterial pH with a glass electrode pH meter

Oxygen Breathing

The effect of breathing 100 per cent oxygen is of value in differentiating pulmonary from other causes of arterial hypoxemia and cyanosis In cyanotic patient with hypoxemia

to pulmonary disease the arterial oxygen saturation rises and may reach 97 per cent or more In cyanotic patients with hypoxemia due to congenital heart disease with a venous arterial shunt breathing 100 per cent oxygen does not significantly raise the arterial oxygen

Circulatory (Perfusion) Function of the Lung

This is determined by cardiac catheterization and intracardiac manometry (p 74) Thus the pressures in the right atrium right ventricle pulmonary artery and pulmonary capillaries are determined The cardiac output may be determined by the Fick principle (p 209) From the cardiac output (CO) and pulmonary artery pressure (PA) the pulmonary resistance (R) can be determined

$$R\ (\text{dynes/sec/cm}^{-5}) = \frac{\text{PA (mean) mm Hg} \times 1332}{\text{CO (cc per sec)}}$$

The effect of exercise on these measurements is ascertained Disturbances in the pulmonary vascular bed due to pulmonary disease may if severe cause a significant *increase in pulmonary resistance* and pulmonary artery pressure at rest and/or with exercise

ETIOLOGY OF CHRONIC COR PULMONALE

Cor pulmonale may occur in any chronic pulmonary disease which produces lesions sufficiently extensive or critically placed An essential requirement is that they so increase the pulmonary vascular resistance that there is a strain on the right ventricle

Pulmonary (Obstructive) Emphysema

Although many chronic pulmonary diseases are capable of causing cor pulmonale pulmonary emphysema is the classic and most common cause This is because of the relatively greater frequency of pulmonary emphysema than that of other diseases which are associated with cor pulmonale Scott and Garvin[91] found cor pulmonale due to emphysema in 50 (6 3 per cent) of 790 autopsied patients who had died of heart disease Parker[170] observed hypertrophy of the right ventricle in 75 per cent and cardiac failure in 44 per cent of 32 cases of uncomplicated pulmonary emphysema In clinical experience of course, *the incidence of cor pulmonale is much lower* since cases studied at autopsy are apt to represent the most advanced stage of this disease

Bronchial Asthma

Bronchial asthma of long standing is usually associated with extensive pulmonary emphysema[9] and may be associated with severe disturbances in pulmonary function[107] and with cor pulmonale, *as denoted by right ventricular hypertrophy and failure*[195]

Pulmonary Tuberculosis

Right ventricular hypertrophy and congestive heart failure result when there is extensive involvement of the lungs and their vascular bed[99 122 1 194] According to Griggs Coggin and Evans,[99] pulmonary tuberculosis was associated with right ventricular hypertrophy in 3 7 per cent and congestive heart failure in 1 8 per cent of 1470 cases, but a higher incidence was noted in the smaller series of Ackerman and Kasuga[1]

Pneumoconiosis

According to Griggs, Coggin and Evans,[99] pneumoconiosis or silicosis a form of pulmonary fibrosis, is associated with a higher *percentage of cases of cor pulmonale* than either pulmonary emphysema or tuberculosis although the absolute number of cases of cor pulmonale due to pneumoconiosis is less Samuelson[188] reported the findings in 83 advanced cases of silicosis, in about 70 per cent of which there were signs of cor pulmonale Thomas[16] described a consistent right ventricular hypertrophy in 50 autopsied cases of pneumoconiosis of coal miners and electrocardiographic changes suggesting right ventricular hypertrophy Cor pulmonale occurs if the lesions are very extensive[7]

Chronic Bronchiectasis Other Pulmonary Diseases

Chronic bronchiectasis is one of the commoner causes of *cor pulmonale* with congestive heart failure *but only when it produces extensive obstructive emphysema*[155]

Cor pulmonale is said to develop in 10 per cent of children dying of *fibrocystic disease of the pancreas*[130 219] owing to the associated bronchiectasis I have observed cor pulmonale with right sided congestive heart failure following *chronic pulmonary suppuration* with perforation into the pleural cavity and chronic empyema

Willius[225] reported a case of cor pulmonale including congestive heart failure secondary to diffuse bilateral *congenital cystic disease of the lungs*

Sarcoidosis

There may be extensive fibrosis of the lungs with involvement of the small pulmonary vessels and eventual involvement and failure of the right side of the heart[187 43 182] Nevertheless, in recent reported series of cases of sar

coidosis there [illegible] only brief mention of the occurrence of cor pulmonale perhaps because of primary preoccupation with pulmonary function studies[11 130 11] The epithelioid granulomata in the lung are invaded and eventually more or less completely replaced by dense collagenous tissue The smaller bronchi and blood vessels become obstructed and eventually destroyed and there is occasionally an obliterative endarteritis The disturbances in pulmonary function which may occur when the fibrosis is extensive may be characterized by restrictive fibrosis by obstructive emphysema or by impaired alveolar capillary diffusion [illegible]

Scleroderma may be associated with extensive fibrosis fibrinoid necrosis and an inflammatory reaction Shuford et al[205] found typical reticulated and linear infiltrations in the roentgenograms of the chest in 5 of 37 patients with scleroderma Pulmonary hypertension and cor pulmonale may occur

Idiopathic Interstitial Fibrosis of the Lung

A number of cases of acute or chronic diffuse interstitial fibrosis of the lung of idiopathic origin[23] including cases of Hamman Rich syndrome[10] and chronic granulomatous pneumonitis of unknown etiology [illegible] are associated with extensive lesions involving the alveolar capillary membranes (Figs 148 149) and producing eventually right ventricular hypertrophy and right sided heart failure[3 191] I have observed several such cases in the past few years

Kyphoscoliosis and Other Thoracic Deformities

Hypertrophy and dilatation of the right ventricle have been found in about 75 per cent of cases of severe kyphoscoliosis[178] [illegible] [121] In Bachman s[8] exhaustive study of kyphoscoliosis he observed that of 154 carefully examined hearts, 56 per cent revealed dilatation and hypertrophy of the right ventricle 26 per cent, of both ventricles and 17 per cent of the left ventricle Fisher and Dolehide[73] described the development of fatal cardiac failure in patients with thoracic deformities especially kyphoscoliosis

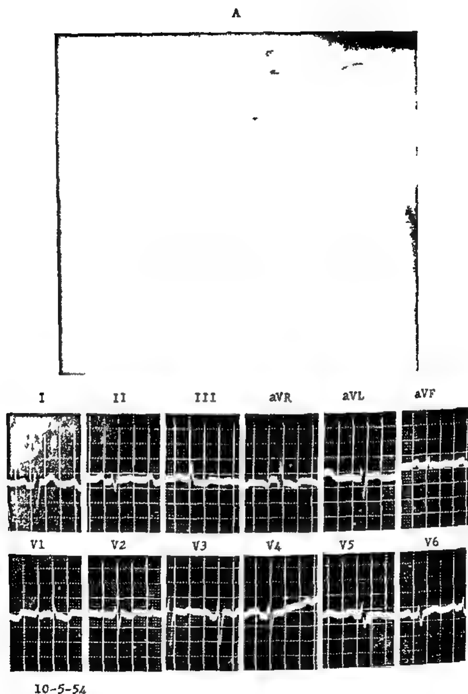
Thoracoplasty

Zimmerman[42] described 5 patients who developed cor pulmonale eight to fifteen years after thoracoplasty The pulmonary artery pressure and pulmonary resistance were greatly increased Cor pulmonale developed even when the contralateral lung was free of disease



Fig 148 *A* Cor pulmonale secondary to interstitial (alveolar-capillary) fibrosis of the lung (Hamman Rich type)

B Microscopic section showing narrowing of alveolar sacs by extreme granulation tissue and fibrotic widening of interalveolar tissue Respiratory alveolar endothelial cells replaced by cuboidal epithelium Alveoli displaced from capillaries by thickened alveolar capillary fibrosis (Courtesy of Dr L Siltsbach.)



B

Fig 149 4 Interstitial fibrosis of lung with alveolar-capillary block and cor pulmonale in woman aged 53 Four years duration Diffuse reticular streaking both lung fields Marked prominence pulmonary artery and hilar vessels

B Electrocardiogram of same patient Right axis deviation indicated by deep S_1 and relatively tall R_3 Tall R in aV_R and V_1 and diphasic or inverted T in V_1 to V_4 indicate right ventricular hypertrophy

Pneumothorax and various forms of pleural pulmonary disease which cause cardiac displacement may occasionally produce circulatory symptoms and electrocardiographic and roentgenologic abnormalities of the heart but rarely if ever cause cor pulmonale [141]

Funnel Chest (Pectus Excavatum)

This is of interest because cardiac abnormalities are often attributed to it [34] but it is only rarely responsible for significant circulatory dysfunction [23a] as in the cases reported by Ravitch[176] and Lyons et al [133] If the external anteroposterior diameter of the chest is less than 6½ inches compression and displacement of the heart are likely to occur [65] Physical examination frequently reveals a functional systolic murmur usually over the pulmonic area and displacement of the apical impulse to the left The importance of funnel chest to the cardiologist lies in the frequent misinterpretation of these signs as indicative of heart disease [14] Roentgenologic examination is diagnostic[65, 157, 17, 8] (Fig 150) In the anterior view the cardiac silhouette appears displaced to the left and the shadow is less dense than normally because of the diminution in anteroposterior mass The heart may seem enlarged but the heart volume is normal and lateral views reveal the anteroposterior narrowing and sternal depression The deformity may be corrected surgically [19, 10]

Extreme obesity in association with somnolence, Cheyne-Stokes respiration, polycythemia and alveolar hypoventilation has been described as a syndrome [8] which is associated with pulmonary hypertension and right ventricular hypertrophy (i e cor pulmonale) in the absence of significant pulmonary disease [117]

Pectus carinatum (pigeon chest) causes no cardiac abnormalities

Diseases of the Pulmonary Arteries Pulmonary Emboli and Thrombosis

Cor pulmonale results from pulmonary arterial disease only when this is very extensive and involves at least two thirds of the cross-sectional area of the pulmonary vascular bed (p 960) Chronic cor pulmonale is most likely to occur in cases of recurrent pulmonary embolization and/or thrombosis As first indicated by Ljungdahl [123] there is probably a chronic form of pulmonary heart disease resulting from chronic pulmonary emboli The cases of right ventricular hypertrophy with intense cyanosis polycythemia and congestive heart failure sometimes termed Ayerza s syndrome and reported by Jump and Baumann [118] Barnes and Yater [16] Means and Mallory [151] and Montgomery [156] were attributed to large organized thrombi in the stem or main primary divisions of the pulmonary artery The frequent site of the thrombus at the bifurcation of the pulmonary artery certain clinical features in the reported

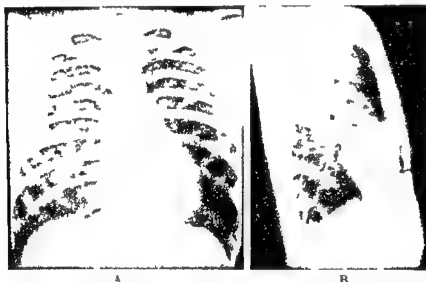


Fig 150 Funnel chest (pectus excavatum) *A* Posteroanterior view Apparent enlargement due to anteroposterior compression of heart Cardiac volume normal Most of cardiac silhouette in left chest Spine shadow prominent Ribs more horizontal than normal
B Lateral view showing sternal depression

histories and the studies by Belt,[21, 22] indicating the comparative rarity of autochthonous thrombi and the frequency of emboli in the main pulmonary arteries, suggest strongly that these were all instances of massive pulmonary embolism which were insufficient to cause death but which produced chronic cor pulmonale Belt[23] described 4 cases of chronic embolization of the pulmonary arteries occurring over a period varying from 3 months to 6 years Similar cases have been reported by others[37, 85, 172, 146, 169, 14] Cases described by Frothingham[64] as progressive thrombosis of the small branches of the pulmonary artery, by Rothschild and Goldbloom[169] as obliterative pulmonary arteritis by Keating et al [119] as chronic massive thromboses of the pulmonary arteries, and perhaps also the case of obliterative arteriolar sclerosis of the lungs by MacCallum[134] and that of multiple pulmonary thrombi by Balboni [8] may all be examples of chronic pulmonary embolization with secondary changes of healing and vascular reaction Cases of chronic cor pulmonale due to amniotic fluid emboli have been reported [135]

Secondary Arteriolar Sclerosis Arteriosclerosis of the small pulmonary arteries and arterioles is probably secondary to pulmonary hypertension associated with diffuse pulmonary disease and not the cause of the pulmonary hypertension [170, 157] This secondary narrowing is at most a minor contributory cause of pulmonary hypertension and cor pulmonale In many instances lesions interpreted as arteriosclerosis of the small pulmonary arteries may represent secondary intimal fibrosis due to healing of pulmonary emboli [14, 197] Such lesions have been produced experimentally by the intravenous injection of thrombotic material [103, 35] Microscopic evidence of arteriosclerosis of the main pulmonary artery is observed commonly in routine autopsies and occasionally the lesions are macroscopically visible However, they are not severe enough to be a factor in causing chronic cor pulmonale [21]

Pulmonary Obstruction with Schistosomiasis Obstruction and inflammation of the pulmonary arterioles due to massive, probably recurrent infection with ova of Schistosoma haematobium or mansoni is capable of producing right ventricular hypertrophy and congestive heart failure [13, 10, 94, 221] Shaw and Ghareeb[204] found pulmonary involvement at autopsy in one third of 282 cases of schistosomiasis In 6 of these the pulmonary obstruction was sufficient to cause a clinical picture resembling so-called Ayerza's syndrome The ova cause injury of the arteriole with consequent acute necrotizing arteriolitis, obstructive endarteritis and perivascular tubercles

Pulmonary Obstruction and Sickle Cell Anemia This disease is often associated with vascular thrombi in the pulmonary arteries and a reactive arteritis [210, 239]

Syphilis and rheumatic fever may produce a pulmonary arteritis but the pulmonary arterial lesions are not themselves a cause of cor pulmonale

Pulmonary Obstruction due to Carcinomatous Lymphangitis or Embolism Cases of occlusion of numerous small pulmonary arteries by tumor emboli as a result of carcinomatous obstruction of the perivascular lymphatics with subsequent vascular thrombosis have been described as resulting in *pulmonale* and right-sided congestive heart failure [88, 140] These lesions produce a subacute rather than a chronic form of cor pulmonale

Primary Pulmonary Hypertension

Primary hypertension is distinguished from secondary hypertension by the absence of intrinsic pulmonary or cardiac disease or of extrinsic causes of pulmonary vascular obstruction As a rule this diagnosis is entertained when cardiac catheterization discloses pulmonary hypertension and no etiologic factor can be discovered [28, 236, 207, 61]

At autopsy, primary pulmonary hypertension is suggested by the finding of right ventricular hypertrophy without evidence of intrinsic cardiac or pulmonary disease or pulmonary emboli [116] Pulmonary vascular lesions may or may not be present Examples of this type have been designated as idiopathic right ventricular hypertrophy by De Navasques et al [53] and others[41, 4] (p 625)

Primary Pulmonary Hypertension with Pulmonary Arterial Occlusive Disease When pulmonary arterial lesions are present these may be regarded as primary and the pulmonary hypertension as secondary to these lesions Examples of such hypertension due to arterial lesions have been noted in connection with recurrent pulmonary emboli, schistosomal and sickle cell arterial lesions It is uncertain whether other occlusive pulmonary lesions of unknown origin represent healed pulmonary emboli which can no longer be identified as such whether they are primary autochthonous

thrombi responsible for pulmonary hypertension or whether they represent a vascular response to intrinsic (humoral or vasomotor) increase in pulmonary arteriolar resistance

Idiopathic Primary Pulmonary Hypertension In some cases of primary pulmonary hypertension there are only minimal vascular changes [2, 4, 84] It has been postulated therefore that there is an essential or idiopathic pulmonary hypertension due to increased pulmonary vasoconstriction analagous to the essential hypertension in the systemic circulation The weak and uncertain vasomotor regulation of the pulmonary arterioles is one of the objections to this concept In some cases of idiopathic pulmonary hypertension the intimal proliferation is of such extent that the pulmonary arterioles are virtually occluded [196] In such cases the occlusive intimal changes appear to be responsible for the pulmonary hypertension

When the vascular lesions are merely intimal thickenings suggesting arteriolosclerosis these may be regarded as secondary to pulmonary hypertension This sequence is less probable when there are thrombotic lesions in various stages of organization [81] Aitchison and Richmond[2] have described a case of primary pulmonary hypertension with occlusive pulmonary arterial lesions which were regarded as secondary to the pulmonary hypertension because postmortem examination indicated that the arterial lesions were recent, whereas the right ventricular hypertrophy was old Necrotizing pulmonary arteritis has also been found at autopsy in cases of primary pulmonary hypertension [13] or of right ventricular hypertrophy of unknown etiology [146] In such cases the possibility of malignant pulmonary hypertension has been considered in analogy to the necrotizing arteriolar lesions secondary to "malignant" or "accelerated" hypertension in the systemic circulation Similar necrotizing pulmonary arteriolar lesions have been found in cases of severe pulmonary hypertension secondary to mitral stenosis [?, 110] and Eisenmenger's syndrome

A distinctive clinical syndrome of primary pulmonary hypertension has been described [?, 2, 4] Actually the findings are those of cor pulmonale without demonstrable pulmonary or cardiac disease The patients are chiefly young adults Exertional dyspnea and weakness, exertional precordial pain and effort syncope[62, 112, 196a] are the outstanding symptoms probably related to an inability to increase the cardiac output and consequent vascular reflexes A systolic murmur is audible in most cases The second pulmonic sound is accentuated The clinical course is unfavorable characterized by right-sided heart failure and occasionally terminating in sudden death There is a report of 3 cases in which death occurred following cardiac catheterization [194] Cyanosis without clubbing may be present usually as a late development The objective clinical, roentgenologic and electrocardiographic findings are determined by the presence of pulmonary hypertension right ventricular hypertrophy and right-sided heart failure On fluoroscopic examination the pulmonary artery segment and hilar vessels are prominent but the peripheral vascular markings are diminished

PATHOLOGY AND PATHOGENESIS OF CHRONIC COR PULMONALE

Insofar as the development of cor pulmonale is concerned we are interested primarily in the pathology of the pulmonary vessels Fundamentally cor pulmonale results from an increase in the pulmonary vascular resistance and the consequent increase in pulmonary blood pressure A variety of mechanisms have been listed to account for increased vascular resistance and pulmonary hypertension (Fig 151) These include (1) anatomic reduction of the pulmonary vascular bed (2) anoxia, which may act by (a) pulmonary vasoconstriction (b) increased pulmonary blood flow or (c) increased blood viscosity (3) increased intraalveolar pressure (4) increased bronchomotor tone (5) bronchial pulmonary shunts, and (6) secondary pulmonary arteriolosclerosis Of these factors the anatomic reduction of the pulmonary vascular bed is by far the most important In some cases anoxia plays an important secondary role The significance of the other facts is less well established

1 Anatomic Reduction of the Pulmonary Vascular Bed

In cases of pulmonary emphysema, the alveolar spaces are enlarged and in many places confluent and the septa are ruptured incomplete atrophic or missing entirely The changes in the alveolar septa result in fibrosis narrowing thrombosis or complete obliteration of capillaries In consequence there is a marked reduction in the total cross sectional area of the available capillary circulation As a

result there may be an increase in pulmonary vascular resistance even at rest, and a consequent pulmonary hypertension, since the cardiac output is normal With exercise, the inability of the pulmonary vascular bed to enlarge as it does normally, results in an increase in the pulmonary blood pressure This occurs only so long as the right ventricular output increases With very severe increase in pulmonary vascular resistance it may be impossible to increase the blood flow through the pulmonary bed, even with an increase in the pulmonary blood pressure

increased pulmonary vascular resistance with consequent pulmonary hypertension has been attributed to (1) diminution in the pulmonary vascular bed due to atelectasis and fibrosis of the affected lung and compensatory emphysema of the unaffected lung tissue, (2) kinking and stenosis of the pulmonary artery In the cases of cor pulmonale due to pulmonary vascular disease, the increased pulmonary resistance is clearly due to the obstruction of pulmonary vascular pathways by emboli, thrombi or narrowing of the lumina by intimal thickening But structural

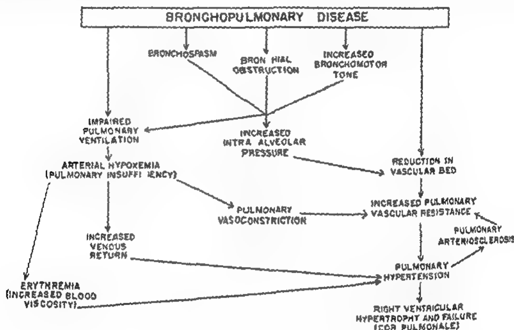


Fig 151 Mechanisms in the production of cor pulmonale

In the cases of pulmonary fibrosis whether idiopathic or associated with sarcoidosis scleroderma or other forms of fibrosis there is an increase in resistance due to compression or replacement of the pulmonary vessels by fibrotic tissue In some cases there is an associated obstructive emphysema with additional reduction in the caliber and number of capillaries The occurrence of increased pulmonary resistance and pulmonary hypertension in cases of chronic tuberculosis, pneumoconiosis, and other bronchopulmonary diseases may be similarly explained by the reduction in the number and caliber of the capillaries or their replacement by fibrous tissue due to the presence of extensive interstitial and alveolar capillary fibrosis or of associated obstructive emphysema In cases of kyphoscoliosis the

changes in the pulmonary vascular bed are not the sole cause of increased pulmonary resistance and pulmonary hypertension because the latter can increase rapidly and sharply following a bronchopulmonary infection and diminish rapidly when the bronchopulmonary infection and associated bronchospasm are relieved

2 Anoxia

Pulmonary hypertension and cor pulmonale may occur in cases of chronic pulmonary disease with or without significant hypoxemia. Therefore, anoxia is not essential to the development of pulmonary hypertension in chronic cor pulmonale In those cases in which anoxia occurs several mechanisms have been invoked to account for its effect in increasing the pulmonary resistance Von Euler and

Liljestrand[223] obtained experimental evidence in the cat indicating that hypoxemia caused pulmonary vasoconstriction and an increase in pulmonary arterial pressure. More recently Nahas et al [184] observed that the cardiac output increased in hypoxic non-narcotized dogs and that the pulmonary artery pressure was raised without an increase in the vascular resistance. Motley et al [161] demonstrated that the inhalation of 10 per cent oxygen will produce significant increase in the pulmonary blood pressure in normal individuals and this effect of hypoxia has been confirmed in normals[80, 11] and in patients with pulmonary emphysema.[2, 3] Doyle and associates[60] noted that the short term hypoxia caused an increase in pulmonary arterial pressure but that the pulmonary capillary pressure remained unchanged while the cardiac output increased. They interpreted these observations as indicating pulmonary vasoconstriction probably as a direct effect of the low oxygen tension of the returning venous blood on the walls of the pulmonary arterioles. Other experiments with breathing of low oxygen mixtures[185, 100] suggest that anoxia may cause local vasoconstriction in those areas of the lung receiving low oxygen mixtures or inadequately ventilated. In view of the evidence that there is poor vasomotor regulation of the pulmonary vessels there is some uncertainty as to the exact mechanism of the observed increase in pulmonary blood pressure during hypoxia. There is even more uncertainty whether this can be applied to the occurrence of pulmonary hypertension in chronic pulmonary diseases.

Another method by which hypoxemia may contribute to an increased pulmonary resistance is related to the occurrence of an increased venous return and an increased cardiac output observed both in short term experiments in which low concentrations of oxygen are inhaled and in direct determinations of the cardiac output in patients with chronic hypoxemia. The increased blood flow and cardiac output are related to a reduction in the peripheral *systemic* resistance, since the systemic blood pressure is unchanged. This reduced *systemic* resistance may be due to a direct effect of hypoxemia on the peripheral vessels. However the increased venous return and consequent increased right ventricular output cannot readily pass through the diminished *pulmonary* vascular bed. The normal diminution in pulmonary vascular resistance that occurs with increased blood flow as in exercise cannot occur in chronic pulmonary disease in which there is an extreme reduction in vascular caliber and in the number of patent vessels. Consequently the increased blood flow associated with hypoxemia, like the increased blood flow associated with exercise results in an increased pulmonary vascular resistance and pulmonary hypertension. Finally in many cases of chronic pulmonary disease with hypoxemia there is a marked polycythemia and an increased viscosity of the blood. This contributes to the resistance to blood flow and may play an accessory role in increasing pulmonary vascular resistance and pulmonary hypertension.

3 Increased Alveolar Pressure

In cases of obstructive pulmonary emphysema there is entrapment of air in the alveoli with consequent increase in air pressure. This may compress the pulmonary capillaries and contribute to the reduction in the pulmonary vascular bed and consequent increase in pulmonary vascular resistance. Animal experiments conducted by Hamilton et al [101] indicated that variations in intraalveolar pressure are effective in temporarily creating variations in vascular resistance.

4 Increased Bronchomotor Tone

Rodbard[198] has reviewed the evidence suggesting that bronchiolar (bronchomotor) tone plays an active part in the regulation of pulmonary blood pressure and pulmonary blood flow. Contraction of the bronchioles may cause trapping of air in the alveoli and increased pressure with compression of the pulmonary capillaries. He points out that although the innervation of the pulmonary vessels is scanty that of the bronchial musculature is rich and that there are large numbers of pressure sensitive muscle spindles of the type found in the carotid sinus.

5 Bronchopulmonary Shunts

The findings of bronchopulmonary vascular shunts in cases of chronic pulmonary disease suggests the possibility that the points of anastomosis may act as sites of increased pulmonary resistance and contribute to pulmonary hypertension [127] but there is no direct evidence substantiating this.

6 Pulmonary Arteriolosclerosis has been discussed (p 982). Arteriosclerotic changes in the small arteries and arterioles of patients with advanced pulmonary emphysema are more frequent and more severe than is usual for normal patients of similar age.[158] Most investigators believe that they are secondary

to the pulmonary hypertension resulting from the vascular lesions in pulmonary emphysema.[157, 183] Arteriosclerosis may narrow the lumen sufficiently to add to the increased pulmonary resistance due to the capillary disturbance.[170]

THE HEART

Increased pulmonary vascular resistance and pulmonary hypertension cause cor pulmonale by increasing the strain and work of the right ventricle (p. 989). The effect of pulmonary hypertension on the right ventricle is similar to that of essential hypertension on the left ventricle. A progressive increase in pulmonary vascular resistance is compensated by a gradual, usually clinically imperceptible dilatation and hypertrophy of the outflow tract of the right ventricle. Heart failure may be due chiefly to the strain imposed by increased pulmonary resistance, but in some cases arterial hypoxemia may contribute to heart failure by causing myocardial anoxia. The right cardiac chambers dilate and undergo further hypertrophy as heart failure progresses.

Anatomically, the characteristic feature of the heart in cor pulmonale is hypertrophy of the right ventricle. A variable degree of right ventricular dilatation is also present, but this is more difficult to evaluate. In cases of right-sided heart failure there is usually also dilatation and occasionally hypertrophy of the right atrium.

Right ventricular hypertrophy in cases of pulmonary emphysema has been demonstrated by weighing the chambers separately according to the method of Muller.[111, 112] By means of linear measurements of the extent of the chambers, Kirch[1, 2] found that the hypertrophy began in the outflow tract of the right ventricle (p. 106), i.e., the anterior half of the chamber extending from the apex to the pulmonary arteries. Right ventricular hypertrophy eventually develops in 25 to 75 per cent of cases of pulmonary emphysema.[1, 4, 95, 170] For simplicity many observers have assumed that the right ventricle is enlarged if its average thickness exceeds 5 mm. Right ventricular hypertrophy may be overlooked if this chamber is not separately weighed or measured, because the weight of the heart as a whole may not be significantly increased. Attention is frequently called to the presence of associated left ventricular hypertrophy in autopsied cases of pulmonary emphysema, in which hypertension, aortic valvular disease and other possible causes of such hypertrophy have been reasonably excluded.[124, 170] This observation should be further investigated and verified before attempts are made to explain it.

PATHOLOGIC PHYSIOLOGY

The functional disturbances in chronic pulmonary disease associated with cor pulmonale may be discussed under the following headings: (1) impaired pulmonary ventilation, (2) impaired aeration of the blood, (3) cardiac output, (4) pulmonary hypertension and (5) right ventricular strain.

1. Impaired Pulmonary Ventilation and Diffusion

The pulmonary diseases responsible for disturbances in ventilation and aeration have been classified into three groups according to pulmonary disturbance:[10] (a) those with obstructive ventilatory dysfunction, (b) those with restrictive ventilatory dysfunction, (c) those with alveolar-capillary or diffusional dysfunction. Frequently two or more of these are associated.

(a) Obstructive Ventilatory Dysfunction. This includes primarily cases of obstructive pulmonary emphysema and bronchial asthma,[107] but obstructive ventilatory dysfunction is often a prominent feature in extensive pulmonary tuberculosis, silicosis, kyphoscoliosis and some cases of sarcoidosis[44] and pulmonary fibrosis.

In this group bronchial or bronchiolar obstruction with alveolar trapping of air plays an important role. The lungs are maintained in a hyperinflated inspiratory position in which the bronchial passageways are most patent. The diaphragms are low. It has been generally stated that there [redacted] a loss of tissue elasticity and a diminished force of elastic recoil in expiration. Studies of the mechanics of respiration in emphysema indicate that the major disturbance [redacted] an increased resistance to air flow and that pulmonary compliance (distensibility) is but little diminished. Increased respiratory rate is inefficient because as a compensation for inadequate ventilation tachypnea greatly enhances airflow resistance. The work of breathing is markedly increased and ventilatory capacity is impaired. There is a striking maldistribution of inspired air to the various alveoli, some being overventilated, many underventilated.[188]

Pulmonary function tests[18, 15, 113, 12] disclose an increase in total lung volume and more significantly an increase in the residual volume, its ratio to total volume rises to 35 to 50 per cent or higher. Alveolar nitrogen after 7 minutes of oxygen breathing exceeds 3 per cent because of poor alveolar distribution of the oxygen and a large residual volume. The maximal breathing capacity and the breathing reserve are diminished. The vital capacity may be less strikingly reduced, but the timed vital capacity is sharply diminished.[196] Bronchospirometry discloses slowing of expiration, "trapping" of air with successive deep breaths and performance of maximum breathing in a high inspiratory position. The minute volume of ventilation is increased by an increase in tidal volume, the rate remaining unchanged or diminished.

(b) Restrictive Ventilatory Dysfunction. This group includes cases of pulmonary disease associated with diffuse fibrosis such as silicosis, fibroid tuberculosis (with minimal emphysema), pulmonary fibrosis secondary to bronchiectasis, some cases of Boeck's sarcoidosis and postradiation fibrosis and kyphoscoliosis. In many cases of silicosis and pulmonary tuberculosis significant obstructive emphysema is associated with the fibrosis.

Restrictive ventilatory function results from destruction or replacement of pulmonary parenchyma by scar tissue. Lung volumes are more or less symmetrically reduced and there is a restriction in the lung's capacity to inflate or deflate. Maximum breathing capacity and vital capacity may be reduced fairly uniformly. But often there is relatively little reduction in maximum breathing capacity when total capacity is greatly diminished, in contrast with the disproportionately greater reduction of M.B.C. in pulmonary emphysema. This suggests that diminished ability to inflate and deflate the lungs in restrictive pulmonary fibrosis may be compensated by increased speed of ventilation.

In the absence of associated emphysema the residual air in these cases is not increased and the ratio of residual air to total volume is normal (20 to 30 per cent). The mean index of intrapulmonary mixing is below 2. The form of the spirogram is normal. Tachypnea and hyperventilation, especially with slight exercise, are characteristic, particularly in severe cases. This is explained as due to more active Hering-Breuer reflexes. The tachypnea may be related to a greatly diminished compliance (increased elastance) with normal airflow resistance. Compensatory hyperventilation is most efficiently accomplished in such cases by increased rate, since vital capacity is low.

(c) Alveolar-Capillary Diffusional Dysfunction (Alveolar-Capillary Block). This group includes cases of diffuse interstitial fibrosis of undetermined etiology, scleroderma of the lung, some cases of pulmonary sarcoidosis and beryllium or other xanthomatous granulomatosis of the lung.[11] These cases are characterized by fibrosis which particularly involves the alveolar-capillary interfaces and interferes with gaseous diffusion.

The vital capacity is reduced, but the maximum breathing capacity may be normal or very slightly diminished. There is a reduction in residual and total volume, but the ratio of residual to total capacity is relatively normal. Bronchospirometry shows a normal pattern. The index of intrapulmonary mixing shows a low nitrogen concentration. The alveolar oxygen partial pressure is elevated to 120 to 150 mm. Hg when the arterial oxygen tension is normal (95 mm. Hg) or only moderately reduced. This high A-a gradient is a measure of impaired diffusion.

2. Impaired Aeration of the Blood

Impaired aeration of the blood in the cases with emphysematous (obstructive) ventilatory dysfunction results in part from subnormal and uneven alveolar oxygenation and in part from a reduction in the capillary bed with consequent faulty perfusion. The inefficient distribution of tidal air often results in disproportionate ventilation of distended alveoli and air sacs with missing alveolar septa which have the poorest blood supply[48, 186] (increased dead space effect). On the other hand, poorly ventilated alveoli are well perfused by capillary blood which leaves the alveoli without adequate aeration (venous admixture effect). This combination of increased dead space and venous admixture effects tends to reduce the arterial oxygen tension and saturation at rest and especially after exercising.

The increased minute volume of respiration compensates for the inefficiency in ventilation and impaired aeration of the blood, but reduces the respiratory reserve. With the enhanced metabolic demands of exercise further respiratory increase is limited or impossible and normal aeration of the blood cannot be maintained. With more advanced

pulmonary emphysema the arterial oxygen of the blood is reduced significantly even when the patient is at rest [114, 146] The effective pulmonary blood flow i e the percentage of pulmonary capillary blood which is oxygenated, was found to average 69 per cent in a group of patients with severe pulmonary emphysema [179]

Although in general, disturbances in ventilation and reduction in pulmonary vascular bed increase concomitantly one or the other may predominate Occasionally anatomic reduction in vascular bed increased pulmonary resistance and pulmonary hypertension cause cor pulmonale before the ventilatory disturbances cause pulmonary insufficiency i e there is cor pulmonale without arterial hypoxemia [55] More often when cor pulmonale develops the pulmonary lesions are severe enough to cause pulmonary insufficiency as well as cor pulmonale and right-sided heart failure [154]

In patients with pulmonary insufficiency and right ventricular failure there is a marked reduction in arterial oxygen saturation The latter hypoxemia is due to and is a measure of the severity of pulmonary insufficiency Congestive heart failure of other etiology is associated with little or no arterial hypoxemia in the absence of pulmonary complications (p 190) Relief of right sided heart failure by digitalis preparations may cause no significant increase in arterial oxygen and no perceptible improvement in the clinical picture because both the hypoxemia and symptomatology are due essentially to the *pulmonary* insufficiency On the other hand, relief of pulmonary insufficiency and the associated hypoxemia may relieve the right-sided heart failure because hypoxemia in some manner increases pulmonary resistance and consequently the pulmonary blood pressure and the work of the right ventricle

Because of the greater diffusibility of carbon dioxide, the hyperventilation in pulmonary emphysema more readily eliminates excessive *carbon dioxide than it maintains adequate* oxygenation Therefore a retention in carbon dioxide occurs less frequently and later than a reduction in arterial oxygen [114] But when the ratio of residual air to total capacity exceeds 45 per cent, both carbon dioxide retention and arterial hypoxemia develop [113, 173] The arterial carbon dioxide tension exceeds 45 mm Hg and there may be a reduction in the pH of the blood It is generally believed that with carbon dioxide retention the sensitivity of the respiratory center is diminished and further carbon dioxide retention is favored [216, 2] But there is evidence that inability to increase ventilation in advanced emphysema is due not to insensitivity of the respiratory center but to mechanical and metabolic factors [31] On the mechanical side, greater respiratory effort becomes limited by distressing dyspnea or fatigue On the metabolic side, increased carbon dioxide production by the muscles of respiration reaches a level which exceeds any increase in carbon dioxide elimination

In the cases of restrictive fibrosis and of impaired alveolar capillary diffusion, hyperventilation may long serve to maintain the arterial oxygen tension at normal levels But hypoxemia becomes marked with exercise, especially in the cases with diffusion dysfunction In advanced cases there is hypoxemia at rest as well as with exercise The arterial carbon dioxide may be diminished owing to hyperventilation, and a gaseous alkalosis may be indicated by a slight elevation of the pH of the blood

Although hypoxemia is *frequently present* in cases of advanced pulmonary disease with cor pulmonale, there may be little or no hypoxemia even in cases of chronic cor pulmonale and heart failure due to obstructive emphysema [55] In general, there is likely to be serious ventilatory insufficiency and deficient arterial oxygenation if the pulmonary lesions are severe and extensive enough to reduce the pulmonary vascular bed and cause cor pulmonale However, cor pulmonale may occur without hypoxemia if the restriction in pulmonary vascular bed outpaces the disturbances in pulmonary ventilation and alveolar capillary aeration Thus pulmonary insufficiency (arterial hypoxemia) may be associated with cardiac insufficiency due to cor pulmonale or the two may be dissociated When pulmonary heart failure and pulmonary insufficiency are associated recovery from *heart failure is not* accompanied by a significant rise in arterial oxygen

3 Increased Cardiac Output

When increased minute volume of respiration no longer compensates sufficiently to maintain a normal oxygen content of the arterial blood other compensatory mechanisms may serve to provide the tissues with an adequate supply of oxygen [114] As in cases of anemia, this may be accomplished by an in

creased cardiac output (minute volume blood flow[148]) In advanced pulmonary emphysema with considerable arterial oxygen unsaturation the speed of the circulation is increased and the venous return thereby augmented This in turn is translated into the greater cardiac output [148, 177, 104]

However, an increased cardiac output is frequently or usually absent in cases of pulmonary heart disease with heart failure, with or without hypoxemia [54, [illegible], [illegible], 1 6, 231] In most cases the cardiac output at rest is normal or reduced In cor pulmonale without hypoxemia the progressive diminution in vascular bed leads to right ventricular failure and the cardiac output may fall These are cases of low output heart failure

Mild or moderate hypoxemia may have no significant effect on the cardiac output, but severe hypoxemia reduces the systemic peripheral resistance increases the venous return and the cardiac output Heart failure may reduce the output somewhat but it is still above normal However even with severe hypoxemia the cardiac output may not rise or may fall if there is so severe a reduction in the pulmonary vascular bed and so great a pulmonary vascular resistance that the right ventricle is unable to expel a normal output of blood through that vascular bed Dexter[54] found that the cardiac output in cor pulmonale was not elevated when the pulmonary "arteriolar resistance rose to approximately four times normal Lewis et al [1 6] reported cases of cor pulmonale with severe hypoxemia and heart failure in which the cardiac output was normal at rest but could not be increased with exercise

4 Pulmonary Hypertension

In advanced pulmonary disease the reduction in number and caliber of the pulmonary capillaries and arterioles results in a progressive increase in pulmonary vascular resistance During the compensated stage of cor pulmonale the right ventricle maintains a normal cardiac output despite increased pulmonary vascular resistance and the pulmonary blood pressure is thus elevated [105, 104] The pulmonary capillary pressure is normal and the pulmonary artery pulmonary capillary gradient is increased [240] Whitaker[21] found the pulmonary blood pressure to range between 8 and 33 mm Hg in patients with cor pulmonale without heart failure between 37 and 59 mm Hg in patients with cor pulmonale in the stage of heart failure The pulmonary diastolic as well as systolic pressure is elevated [[illegible]] Whereas the pulmonary blood pressure is unaltered by exercise in the normal individual despite the increase in cardiac output, in patients with extensive pulmonary disease and a greatly reduced pulmonary vascular bed the increased blood flow cannot be readily accommodated and the blood pressure rises [103, 181]

Other factors, besides a reduction in the pulmonary vascular bed which increase pulmonary vascular resistance and lead to pulmonary hypertension have been discussed (p 987) In clinical practice hypoxemia is particularly important Commonly in patients with compensated cor pulmonale a bronchopulmonary infection producing or intensifying hypoxemia, causes a sharp rise in pulmonary *blood pressure and induces right-sided* heart failure Recovery from the infection is followed by increased arterial oxygen saturation reduction in pulmonary arterial pressure and disappearance of heart failure [47, 162]

5 Right Ventricular Strain

The development of pulmonary heart disease is related specifically to the narrowing and obliteration of the pulmonary vessels and the consequent pulmonary hypertension Pulmonary insufficiency without pulmonary hypertension does not cause cor pulmonale Pulmonary heart disease or cor pulmonale may be said to be present only when there is evidence of right ventricular strain as indicated by hypertrophy of the right ventricle or evidence of pure right ventricular failure

Right ventricular strain is due to an increase in pulmonary resistance which tends to cause incomplete right ventricular emptying and a diminution in stroke output Compensatory dilatation and subsequent hypertrophy restore the stroke output despite the elevation in pulmonary resistance [7] During the compensated phase measurements by intracardiac catheterization have shown an elevation in right ventricular systolic and pulmonary arterial pressure When right heart failure occurs the right ventricular diastolic and the right atrial pressure also rise The high pressure in the right ventricle in cases of pulmonary heart disease by interfering with coronary drainage into that chamber, may impair the blood supply to the hypertrophied right ventricle and accelerate heart failure [[illegible]] but it is questionable whether this is a significant factor in the production of right ven

pulmonary emphysema the arterial oxygen of the blood is reduced significantly even when the patient is at rest [114, 143] The effective pulmonary blood flow, i.e., the percentage of pulmonary capillary blood which is oxygenated, was found to average 69 per cent in a group of patients with severe pulmonary emphysema [179]

Although in general disturbances in ventilation and reduction in pulmonary vascular bed increase concomitantly, one or the other may predominate. Occasionally anatomic reduction in vascular bed, increased pulmonary resistance and pulmonary hypertension cause cor pulmonale before the ventilatory disturbances cause pulmonary insufficiency, i.e., there is cor pulmonale without arterial hypoxemia [55] More often when cor pulmonale develops the pulmonary lesions are severe enough to cause pulmonary insufficiency as well as cor pulmonale and right-sided heart failure [184]

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3 Increased Cardiac Output

When increased minute volume of respiration no longer compensates sufficiently to maintain a normal oxygen content of the arterial blood, other compensatory mechanisms may serve to provide the tissues with an adequate supply of oxygen [4] As in cases of anemia this may be accomplished by an in

manifestations are due to the disturbances in ventilation and perfusion and to pulmonary insufficiency which dominate the clinical picture and overshadow the features of right ventricular failure

With the development of right ventricular failure the liver becomes enlarged and tender There may be gallop rhythm and a systolic murmur over the lower sternum the latter due to functional tricuspid insufficiency

Peripheral edema appears and occasionally ascites The course of heart failure is of relatively short duration and progressively unfavorable In the series of cases studied by Scott and Garvin[301] 86 per cent died of their first attack of cardiac failure In some instances I have seen death from chronic pulmonary emphysema (pulmonary failure) attributed erroneously to congestive heart failure because of a sudden intensification of cyanosis dyspnea and cough In these cases the cause of death was an unrecognized acute terminating bronchopulmonary infection In other cases however such an infection by increasing pulmonary vascular resistance and the strain on the enlarged right ventricle may precipitate congestive heart failure But heart failure precipitated by an acute bronchopulmonary infection is usually reversible and early and adequate treatment may alleviate the pulmonary insufficiency and abolish the heart failure

Circulatory Measurements

The venous pressure in uncomplicated emphysema is usually normal[2, 6] In severe cases with elevated intrapleural pressure the venous pressure may also be elevated probably due to the hindrance to venous inflow presented by the rise in intrapleural pressure[125] An asthmatic attack may further elevate the venous pressure in patients with advanced emphysema but Oppenheimer and Hitzig[169] observed normal venous pressures during paroxysms of bronchial asthma in patients without cardiac disease The development of right ventricular enlargement in cases of pulmonary emphysema is not marked by any change in venous pressure but a distinct rise occurs when the right ventricle fails Measurements by means of intracardiac catheterization showed normal right atrial and right ventricular diastolic pressures but elevated right ventricular systolic blood pressure in cases of chronic pulmonary emphysema without heart failure In the presence of heart failure the right atrial and the right ventricular diastolic pressures were also elevated[27, 18]

The *circulation time* is normal in uncomplicated pulmonary emphysema[2, 6, 215] even during an attack of bronchial asthma[163] and it remains normal during the compensated stage of chronic cor pulmonale However when the emphysema is advanced enough to induce intense arterial anoxemia the circulation time may be significantly reduced probably owing to peripheral vasodilatation as in cases of severe anemia During the stage of right sided heart failure there is a prolongation in both the arm to tongue (saccharin) time and in the arm to lung (ether) time The difference between these two times i e the lung-to-tongue time, is normal because all of the delay occurs between the systemic veins and the pulmonary capillaries When there is severe emphysema the delay in circulation due to heart failure may be neutralized by the acceleration due to pronounced arterial anoxemia On the other hand polycythemia with increased viscosity of the blood tends to slow the circulation

The *circulating blood volume* may be normal in mild cases of emphysema heart but is increased in severe cases with arterial anoxemia and polycythemia[174, 6] The increased blood volume is due to the increase in erythrocytes However in the presence of heart failure the plasma volume may also be augmented[69, 1, 8] The *hematocrit* is increased

Roentgenology

Compensated Stage of Cor Pulmonale There may be roentgenologic evidences of pulmonary hypertension i e dilatation of the pulmonary artery and its branches but enlargement of the right ventricle is rarely demonstrable The recognition of the latter is made difficult by the low diaphragm with consequent median position of the heart and by the barrel shaped chest which permits such enlargement to occur in an anterior direction without displacement of the cardiac borders to the left or right The following roentgenologic alterations in emphysema heart disease have been described[171, 184, 136]

1 Exaggeration of the hilar shadows, due to the enlargement of the main pulmonary arteries and their chief subdivisions

2 Prominence or convexity instead of the normal concavity of the left middle (pulmonary) arc

3 Enlargement of the right ventricle This may be demonstrable by angiocardiography,

which discloses a convexity of the interventricular septum to the left instead of to the right as in the normal heart [12] In the lateral view, in which the right ventricle forms the anterior border of the silhouette there may be encroachment on the retrosternal space

According to Binhold[24] there is usually an increase in the total volume of the emphysematous heart, as determined by Kahlstorf's method The left atrium is normal, but the left ventricle may appear slightly enlarged, probably due to independent disease or anoxemia

Decompensated Stage of Cor Pulmonale In addition to the above with the development of heart failure the right atrium may become enlarged as indicated by an increase in the right lower silhouette and of the entire transverse diameter The shadow of the superior vena cava may also become wide and prominent The enlargement of the right ventricle is more noticeable and involves the inflow as well as the outflow tract (p 106)

Electrocardiogram

The electrocardiogram of chronic cor pulmonale may disclose no abnormality or the following changes due to a vertical position of the heart and/or right ventricular hypertrophy [201, 171, 244] Distinct evidence of right ventricular hypertrophy is observed only in advanced chronic cor pulmonale Since patients with chronic pulmonary disease frequently have a vertical, clockwise rotated heart some of the electrocardiographic changes attributed to right ventricular hypertrophy may be due to the altered position of the electrical axis The following changes are often observed

(1) Prominent peaked P waves in leads II and III and V_F with P_3 higher than P_1 Negative P wave in V_L There may be a prominent atrial T wave
(2) S_1 is usually prominent and R_3 tall S_2 and Q_3 may be present denoting clockwise rotation of the heart
(3) T_3 is often inverted and T_2 may be isoelectric or inverted, T is also inverted in V_F
(4) In the chest leads (a) There may be a tall R in V_1 and aV_R, (b) the peak of R is delayed in right precordial leads to 0 035 second or more after the onset of QRS, (c) the R wave is small and the S deep in the left precordial leads
(d) The T and P waves are inverted in the right precordial leads

The relative importance of the position of the heart and of hypertrophy and dilatation of the right ventricle in the production of these changes is discussed elsewhere (p 113) Distinctive electrocardiographic signs of right ventricular hypertrophy are correlated with the degree of pulmonary hypertension,[118] and usually are present when the mean pulmonary artery pressure exceeds 30 mm Hg and the mean pulmonary resistance exceeds 750 dynes/sec /cm^{-5} [90]

DIAGNOSIS OF CHRONIC COR PULMONALE

The diagnosis of chronic cor pulmonale is based on recognition of (1) underlying pulmonary disease and (2) right ventricular enlargement with or without failure, and on (3) exclusion of mitral stenosis and other cardiac causes of right ventricular enlargement

The history and physical and roentgenologic examination of the chest will usually reveal the presence and nature of the pulmonary disease and exclude primary cardiovalvular disease It is often difficult to differentiate uncomplicated emphysema and other pulmonary disease from compensated cor pulmonale The diagnosis of the latter requires demonstration of right ventricular hypertrophy as indicated by the roentgenologic and electrocardiographic signs These usually disclose only extreme degrees of right ventricular hypertrophy, hence compensated cor pulmonale is usually difficult to diagnose

When evidence of right sided heart failure is added to that of the primary pulmonary disease, the diagnosis of pulmonary heart disease is more definite However dyspnea cyanosis and even a slight elevation of venous pressure may be due to emphysema alone Hepatic enlargement and subcutaneous edema in addition to a pronounced elevation in venous pressure and prolongation of circulation time are indicative of right sided heart failure Extreme intensification of cyanosis and dyspnea is usually due to pulmonary insufficiency and not to the development of right sided heart failure

TREATMENT

In the compensated stage of chronic cor pulmonale, treatment is concerned only with the underlying emphysema or other pulmonary disease But even in the presence of cor pulmonale with heart failure treatment of the pulmonary disease may be of primary im

portance As in cases of heart failure due to hyperthyroidism, anemia beriberi arteriovenous fistula or active rheumatic fever therapy of heart failure may give a satisfactory clinical result only if the primary disease is controlled or ameliorated Therefore it is important to know the type and extent of the underlying pulmonary disease in cor pulmonale Treatment of each individual pulmonary disease is outside the scope of this discussion However certain therapeutic measures which apply to the diseases associated with obstructive emphysema are not employed in diseases associated with pulmonary fibrosis and vice versa

Antibiotics

Frequently the development or marked intensification of symptoms of cor pulmonale with heart failure is precipitated by a bronchopulmonary infection with or without increased bronchial spasm edema inflammation and obstruction [11] Therefore *antibiotics* are of the greatest importance in the therapy of such cases Smears and cultures of sputum should be made to determine the causative organisms and their sensitivity But penicillin streptomycin and broad spectrum antibiotics and/or sulfonamides should be administered as soon as specimens are obtained Changes in antibiotics or their dosage will be determined by the clinical response and the results of bacteriologic study Serious pulmonary and cardiac insufficiency is most likely to be reversible when a precipitating factor such as a bronchopulmonary infection is discovered and controlled

Bronchodilators

Epinephrine 1 per cent or Isuprel 1 200 should be given by spray or as an aerosol with a positive pressure apparatus[159] in cases of obstructive emphysema especially when there is an associated bronchospastic bronchitis Ephedrine in 20 mg doses by mouth Isuprel (isopropylarterenol) sublingually 5 or 10 mg epinephrine hypodermically or aminophylline 0 25 to 0 5 gm intravenously may have to be administered if there are associated severe episodes of bronchial asthma or bronchospasm Antihistamine drugs are rarely of benefit Expectorants such as potassium iodide may be given as adjuvants to the bronchodilators Pharyngeal secretions should be aspirated Rarely bronchoscopy is essential for relief of bronchial obstruction by mucous plugs and may be lifesaving Amelioration of distressing cough may appear desirable but opiates are contraindicated and codeine or Hycodan (dihydrocodeinone) should be prescribed cautiously The cough will be best controlled by elimination of the infection and the use of bronchodilators and expectorants In some cases of pulmonary disease associated with bronchiectasis postural drainage should also be employed Morphine is contraindicated because it causes severe respiratory depression with consequent accumulation of carbon dioxide in the blood carbon dioxide narcosis coma and occasional fatalities in patients with obstructive emphysema and pulmonary insufficiency

Corticosteroid Hormones

These provide dramatic relief of symptoms and occasional improvement in pulmonary function in many cases of idiopathic pulmonary fibrosis, sarcoidosis and other forms of pulmonary fibrosis in which there is impairment of alveolar capillary diffusion [3 8] They are also dramatically effective whenever intractable bronchial asthma or bronchospastic bronchitis is associated with bronchopulmonary disease

Oxygen Therapy

Oxygen therapy is considered whenever there is severe dyspnea and particularly when there is associated hypoxemia and cyanosis However whereas it may be extremely beneficial in cases of alveolar capillary fibrosis with impaired diffusion and in cases of restrictive pulmonary fibrosis oxygen therapy is dangerous in cases of advanced obstructive emphysema with marked carbon dioxide retention In the latter cases the respiratory center is thought to become relatively insensitive to carbon dioxide and to depend on hypoxemia for its stimulation With the administration of oxygen arterial oxygen tension rises and the hypoxemic stimulus is removed Thereupon respiration is depressed carbon dioxide accumulates and usually when the pCO_2 exceeds 100 mm Hg and the pH is less than 7 2 carbon dioxide narcosis occurs [230] Increased respiratory acidosis (carbon dioxide retention) following the breathing of 100 per cent oxygen was found to be rare in emphysematous patients whose timed (3 minute) vital capacity was more than 50 per cent above the predicted value [83] But with increasing impairment of pulmonary ventilation as indicated by greater reductions of the timed vital capacity there was a progressively increased incidence of

respiratory acidosis following oxygen breathing In addition, breathing pure oxygen by the patient with pulmonary emphysema and hypoxemia results in a diminution in respiratory volume in pulmonary vascular resistance pulmonary artery and pulmonary "capillary" pressure and a reduction in cardiac output[34]

Carbon dioxide narcosis is manifested by mental confusion, occasional mania increasing stupor, coma and death[56, 46, 230] It may occur after relatively brief periods of oxygen administration e g an hour or two in an oxygen tent If oxygen therapy is administered to patients with obstructive emphysema, it should be given if at all, only for brief interrupted periods and with careful and continued observation of the clinical response Therapy should be carried out preferably with control by determination of the blood gases There is evidence that following treatment with bronchodilator drugs antibiotics and intermittent positive pressure breathing, not only is the arterial oxygen saturation increased and hypercapnia diminished but the sensitivity of the respiratory center to carbon dioxide is improved[95]

Intermittent Positive Pressure Respirators

On the other hand, oxygen may be administered to relieve hypoxemia in patients with obstructive emphysema provided artificial aids to respiration are simultaneously employed[9, 131] A Drinker Collins respirator may be used during oxygen therapy to increase alveolar ventilation This prevents increased arterial carbon dioxide tension and gaseous acidosis despite the tendency of the oxygen to cause respiratory depression The respirator also promotes bronchial drainage and helps provide an adequate airway Other simpler artificial respirators may be used to provide intermittent positive pressure breathing,[159, 202] such as the Bennett pressure therapy unit or a pneumatic balance resuscitator (PBR), Burns model These devices are effective in a comatose patient as well as in one who can cooperate Intermittent positive pressure therapy has been used effectively to relieve carbon dioxide narcosis[166] Exsufflation with negative pressure has been effected by an apparatus producing intermittent positive and negative pressure breathing thus promoting ventilation and eliminating mucoid and mucopurulent secretions[41, 203] Recent studies of the comparative value of intermittent positive pressure breathing (IPPB) alone nebulized bronchodilators alone and IPPB with nebulized bronchodilators in chronic emphysema suggest that in the patients studied the nebulized bronchodilators alone were responsible for the beneficial effects[238, 125b]

Other means have been employed to aid ventilation in obstructive emphysema with or without pulmonary or cardiac insufficiency Respiratory exercises[153, 55] and an abdominal belt have been recommended[1, 5, 11] Pneumoperitoneum has been induced to raise the diaphragm and thus promote ventilation[83, [illegible], 241]

Treatment of Heart Failure

Right sided heart failure is treated by rest digitalization low sodium intake and diuretics

Digitalis is indicated as in other forms of heart failure Its efficacy can be demonstrated by manometric studies during cardiac catheterization for the cardiac output is increased and the elevated right ventricular diastolic pressure may be reduced to normal by the intravenous administration of Digoxin[89, 97] Frequently the clinical status of the patient improves very little, despite the administration of digitalis and the alleviation of heart failure This is because of the persistent pulmonary insufficiency which dominates the clinical picture When the arterial oxygen tension rises because of control of a bronchopulmonary infection and improved ventilation, i e, when the pulmonary insufficiency is alleviated, there may be a dramatic clinical improvement Relief of the pulmonary infection, by reducing the pulmonary resistance may also relieve the strain on the right ventricle and permit recovery from right sided heart failure

There has been some disagreement as to the indication for *phlebotomy* in the treatment of cor pulmonale with heart failure It is not indicated as a rule in the cases without hypoxemia In cases of cor pulmonale with marked hypoxemia, as indicated by cyanosis, and with polycythemia, the polycythemia is regarded as compensatory for the hypoxemia Hence removal of blood has been regarded as undesirable because this would further reduce the impaired oxygen transport of the blood Clinical experience in cases of cor pulmonale with severe pulmonary and cardiac insufficiency has convinced me of the benefit, some-

times striking of phlebotomies when carried out as follows Phlebotomy is not performed during the acute stage of pulmonary insufficiency when therapy consists chiefly of antibiotics, bronchodilators, etc When the pulmonary insufficiency is alleviated complete recovery [redacted] markedly accelerated by multiple small phlebotomies of 250 cc each, several days apart

Mercurial diuretics may be employed in the presence of right sided congestive heart failure especially with edema

Diamox a carbonic anhydrase inhibitor has been used both as a diuretic and because it promotes the renal excretion of bicarbonate[163, 199] [redacted] Fishman et al[77] observed that Diamox reduced the arterial blood P_{CO_2} decreased the alkaline reserve facilitated clearing of the sensorium and reduced the hazard of carbon dioxide narcosis Bell et al[0] reported that Diamox improved alveolar ventilation as measured by increased P_{O_2} and decreased P_{CO} but caused only temporary symptomatic improvement Diamox is not indicated for patients without CO_2 retention at rest Diamox therapy should be regarded as an adjunct to treatment with artificial respirators bronchodilators and antibiotics rather than as a primary or major therapeutic factor Diamox may be administered orally in doses of 250 or 500 mg daily in a single morning dose for 5 consecutiv[redacted] days with a rest period of 2 days each week Heiskell et al[106] administered 10 mg per kilogram of body weight every [redacted] hours for four days to 4 patients with chronic emphysema and respiratory acidosis In all four there was significant improvement in pulmonary function increased exercise tolerence decreased dyspnea on exertion and lowered levels of plasma bicarbonate

Salicylates

The intravenous administration of 6 to 8 gm of sodium salicylate over a period of one hour increases the sensitivity of the respiratory center to carbon dioxide lowers the arterial P_{CO_2} raises the arterial oxygen saturation and the pH of the arterial blood in patients with obstructive emphysema[2, 5] Hypercapnia increased by breathing oxygen is ameliorated by intravenous sodium salicylate whereas oral salicylates give variable results Intravenous salicylates may have therapeutic value in pulmonary emphysema with CO_2 retention

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Chapter 40

THE HEART IN HYPERTHYROIDISM

Hyperthyroidism is an important etiologic factor in the production of atrial fibrillation cardiac enlargement and congestive heart failure but there is still considerable uncertainty whether hyperthyroidism per se is responsible for these manifestations In short, it is uncertain whether there is a specific etiologic type of heart disease caused by hyperthyroidism, or whether the latter is merely a contributory or precipitating factor in individuals already predisposed by coincident heart disease

The term thyroid heart disease is restricted to cases in which hyperthyroidism is associated with recurrent paroxysmal or established atrial fibrillation or with congestive heart failure Since many symptoms such as palpitation and tachycardia dyspnea and precordial distress are commonly observed with uncomplicated hyperthyroidism their presence is not in itself sufficient to warrant the diagnosis of heart disease

In the great majority of cases of thyroid heart disease there has been found evidence of associated coronary (atherosclerotic) hypertensive rheumatic or syphilitic heart disease Kepler and Barnes[62] found organic heart disease in 18 (67 per cent) of 27 fatal cases of hyperthyroidism in which there had been evidence of congestive *heart failure Maher* and Sittler[64] reviewed a series of 180 cases of hyperthyroidism in 75 per cent of which they found complicating organic heart disease Furthermore in all of the 38 cases in which congestive heart failure was present and in 41 out of 42 cases in which atrial fibrillation was encountered, there was independent organic heart disease Therefore with one possible exception thyroid heart disease in this series was always associated with an underlying independent organic cardiac disease The great frequency if not the invariable association of organic heart disease the absence of consistent or convincing pathologic evidence of structural cardiac damage due to hyperthyroidism (p 1003) and the reversibility of the cardiac manifestations of hyperthyroidism have given rise to the belief that a characteristic form of heart disease due exclusively to hyperthyroidism does not exist

ETIOLOGY AND PATHOGENESIS

Cause

Most of the symptoms of uncomplicated Graves disease including the circulatory disturbances may be attributed to an excessive production and dissemination of thyroid hormone However the exact mechanism by which the cardiac disturbances are induced is uncertain In addition there is evidence that the pituitary gland the diencephalon and hypothalamus and the adrenal and sympathetic nervous system may be concerned in the production of some of the manifestations of Graves disease and similarly these organs and tissues may also influence the heart and circulation

Age and Sex

Uncomplicated hyperthyroidism is most common between the ages of 20 and 40 [73, 46] In contrast thyroid heart disease is exceptional before the age of 40 and in the series of 108 cases reported by Barker et al,[5] the average age was *51 and a half These* figures stress the importance either of a prolonged duration of the hyperthyroidism or of the appearance of coronary atherosclerosis in later years in the production of the so called thyroid heart

Females predominate in a ratio of 5 to 1 in uncomplicated Graves disease this predominance is reduced to 2 to 1 in cases of thyroid heart disease

MECHANISM

We are concerned here primarily with the mechanism by which atrial fibrillation cardiac enlargement or heart failure i e thyroid heart disease, develops in instances of pre-

viously uncomplicated Graves' disease. Two general possibilities should be considered.

1 Coexistent Heart Disease and Hyperthyroidism

Coexistent independent heart disease reduces the cardiac reserve but compensation is maintained for the ordinary demands placed upon the heart. With the advent of hyperthyroidism certain alterations occur which in one way or another (see below) increase the demands on the heart to a degree which the diseased heart can no longer meet. Cardiac enlargement, cardiac failure and atrial fibrillation then develop. These are all manifestations which might have appeared eventually in the absence of hyperthyroidism, but which develop earlier because of hyperthyroidism.

Conversely, in many instances hyperthyroidism antedates independent heart disease due to hypertension and coronary atherosclerosis. The normal heart for many years is capable of adjusting itself to the requirements imposed by excessive thyroid secretion and increased metabolism. But with the added burden of hypertension and the diminished cardiac efficiency due to coronary ischemia and myocardial anoxia, the heart is no longer able to maintain its normal size and remain compensated. Cardiac enlargement, atrial fibrillation and congestive heart failure are ultimate consequences.

2 Hyperthyroidism as an Exclusive Cause of Heart Disease

The second possibility also exists that prolonged and severe hyperthyroidism may by itself produce atrial fibrillation, cardiac enlargement and failure in the absence of any independent cardiac disease.

METHODS BY WHICH HYPERTHYROIDISM MAY AFFECT THE HEART

1 Effects of Thyroid Hormone on Heart Muscle

The thyroid hormone may impair the heart muscle by direct effects. Since the heart participates in the general increase of tissue metabolism, its oxygen requirement is augmented. This requirement is usually satisfied by an increased coronary flow secondary to a reduction in coronary arterial resistance.[8, 9] The depletion of glycogen in the heart muscle[1] in experimental hyperthyroidism has been attributed to relative anoxia.[78] There is experimental evidence that thyroid extract or thyroxin acts directly on heart muscle to cause tachycardia.[62, 63] However, these findings are inadequate to permit a conclusion that atrial fibrillation or heart failure in clinical hyperthyroidism is the result of a direct cardiac effect of the thyroid hormone.

2 Excessive Sympathico Adrenal Stimulation

Resemblances between the clinical manifestations of hyperthyroidism and those caused by stimulation of the sympathetic nerves or the administration of epinephrine suggest that the cardiac disturbances in Graves' disease may be due to exaggerated stimulation of the sympathico adrenal system. There is, in fact, evidence that the thyroid hormone sensitizes the sympathetic system to the action of epinephrine. In dogs made hyperthyroid by thyroid feeding there were consistently greater increases in oxygen consumption, cardiac rate and cardiac index with infusion of epinephrine or norepinephrine than occurred with the same infusions in euthyroid dogs.[14] These observations were interpreted to indicate that the cardiovascular effects of thyrotoxicosis are not due to a direct effect of thyroid hormone but rather to augmentation of the physiologic effects of epinephrine or norepinephrine by thyroxin.

Careful analysis discloses that the resemblance between the symptoms of Graves' disease and the effects of sympathetic adrenal stimulation is superficial and incomplete. For example, the cutaneous vasoconstriction with consequent pallor and coldness resulting from sympathetic stimulation contrasts notably with the cutaneous vasodilatation and warmth of hyperthyroidism. The tendency to diarrhea is a parasympathetic not a sympathetic effect. The exophthalmos attributed to excessive cervical sympathetic tone has a different pathogenesis.[75] Although sympathetic stimulation and epinephrine could account for tachycardia and are capable of producing ventricular fibrillation experimentally, they do not cause atrial fibrillation.

3 Disturbed Circulatory Dynamics

The most plausible explanation for the effects of hyperthyroidism on the heart is that altered circulatory dynamics impose an excessive cardiac strain. These altered dynamics (infra), which are in part compensatory adjustments to the elevated metabolism, increase the work of the heart and its need for oxygen and diminish its efficiency. In the presence of associated organic heart disease or with the development of coronary atherosclerosis in

middle life these hyperthyroid strains lead to atrial fibrillation and congestive heart failure

PATHOLOGIC PHYSIOLOGY

Increased Metabolism and Oxygen Consumption

An elevated basal metabolism, exceeding normal by 30 to 75 per cent or more, is the basic physiologic change in hyperthyroidism This denotes an increase in oxygen consumption As we shall see, this abnormal tissue oxygen requirement is met by a corresponding increase in minute volume (cardiac output) and not by increased oxygen utilization for the arteriovenous oxygen difference is diminished[63, 9]

Increased Heat Production

This is a consequence of increased metabolism and is disclosed clinically by a warm flushed skin A number of chemical hormonal and nervous compensatory mechanisms are called into action to maintain a constant temperature despite the increased heat production The latter by warming the blood excites nerve centers (hypothalamus and spinal cord) which stimulate the secretion of sweat perhaps also heat receptors in the skin reflexly assist this mechanism The warm sweat (vasodilatation of the skin capillaries) found in hyperthyroidism contrasts with the cold sweat found in psychoneurotic patients or those in shock in whom there is cutaneous vasoconstriction About 6 per cent of the cardiac output flows through the skin in patients with Graves' disease instead of the normal 3 per cent

Increased Cardiac Output (Minute Volume)

An increased cardiac output is characteristic of Graves' disease [4, ■, ■] Like many other physiologic adjustments it represents on the one hand a compensatory process by which the circulation attempts to keep pace with the increased metabolic needs and increased heat production of hyperthyroidism while on the other hand its useful effects are partially vitiated by the strain it imposes on the heart

When heart failure complicates hyperthyroidism the cardiac output falls somewhat but in absolute values it is still abnormally high[10, 40] (high output failure) Occasionally when heart failure is severe the fall in cardiac output may reduce it to within the normal range The response of the cardiac output to exercise is varied In uncomplicated hyperthyroidism there is an abnormally high increase in response to exercise[10] In some cases complicated by heart failure there may be a high resting output with a fall during exercise In other hyperthyroid patients whose cardiac output has been diminished to normal values by severe heart failure there may be no change in output with exercise[40a]

In the normal individual increased cardiac output, e g, during exercise is accomplished by both an increase in cardiac rate and an increase in stroke volume the better trained the individual, the less is the tachycardia and the greater the relative importance of the increased stroke output In patients with hyperthyroidism tachycardia is a cardinal feature the accelerated pulse rate corresponding closely in degree to the elevated metabolism In most if not all cases of hyperthyroidism the increased heart rate is itself capable of accounting for the observed increase in cardiac output By means of the cardiotachometer Boas[13] observed that the average sleeping pulse rate in normal subjects was 58 per minute, while that in patients with Graves disease averaged 89 an increase of 53 per cent which corresponds closely with observed average increases in both the basal metabolism and the cardiac output The tachycardia may be due to direct action of the thyroid hormone on the heart muscle or it may be a consequence of the Bainbridge reflex initiated by the increased venous return

Stroke Output

While these considerations suggest that the stroke output in Graves disease need not be elevated to explain the augmented cardiac output, direct determinations have not yielded consistent results [4] Fullerton and Harrop[34] noted a reduction in the systolic output as well as in the minute volume in ■ patients with Graves disease after thyroidectomy However the average systolic output before operation in these patients was 57 cc which was slightly less than Grollman s average of 62 cc for normal subjects From these figures it is apparent that the preoperative elevation in cardiac output was due to tachycardia and the reduction after operation was entirely or almost entirely caused by a reduction in the heart rate Bansi[3] found that the stroke volume tended to be diminished in patients with Graves' disease While *Liljestrand and Stenstrom*[67] observed a striking elevation in the cardiac output per minute in 11 cases of uncomplicated Graves disease the average out-

put per beat was only 63 cc and the range from 49 to 83 cc corresponding to Grollman's average of 62 cc and range of 38 to 84 cc for normal subjects Even with allowance for certain inconsistencies these observations strongly indicate that the stroke volume in Graves disease is neither significantly nor frequently increased and that it is a relatively unimportant factor in the augmentation of the cardiac output The stroke volume has been considered in some detail because it is an indirect measure of the diastolic tension and of the length of the cardiac fibers in diastole which in turn are related to the development of cardiac dilatation and hypertrophy

Increased Venous Return Peripheral Vasodilatation and Increased Blood Flow

The increased minute volume is itself the consequence of an enlarged venous return Heightened tissue metabolism yields an excess of local metabolites which in turn dilate small vessels establish arteriovenous shunts and lead to an accelerated venous return of blood from the periphery to the heart Roberts and Griffith,[90] with the aid of the capillary microscope observed that most of the cutaneous capillaries in the forearms were dilated in hyperthyroidism The peripheral blood flow, measured by several observers using different methods was uniformly found to be increased in patients with hyperthyroidism [100, 27]

Diminished Circulation Time and Increased Blood Volume

The minute volume (cardiac output) varies with the velocity of blood flow and with the circulating blood volume Actually both of these factors have been found to be increased in patients with hyperthyroidism A heightened velocity of blood flow i e a *diminished circulation time,* was demonstrated by Blumgart, Gargill and Gilligan[12] with the aid of radium C and by Tarr, Oppenheimer and Sagar[101] with the aid of Decholin The circulation time from arm to tongue is usually between 7 and 10 seconds in contrast to the normal of 10 to 16 seconds This acceleration of the circulation probably results from peripheral arteriovenous shunts caused by vasodilatation due to the accumulation of increased metabolites An augmented circulating blood volume was determined by Rowntree and Brown[92] with the use of Congo red, by Chang[19] with the use of carbon monoxide, and by Gibson and Harris[37] with the aid of Evans blue However, the increase in blood volume averages only about 10 per cent [34] On the other hand, the speed of circulation increases 30 to 70 per cent and can account for almost all of the increase in venous return and cardiac output [21]

Relations of Altered Circulation to Thyroid Heart Disease

To what extent are these circulatory adjustments in hyperthyroidism responsible for the manifestations of thyroid heart disease namely, atrial fibrillation cardiac enlargement and congestive heart failure? The tachycardia which is uniformly present in uncomplicated hyperthyroidism is rarely of sufficient degree to induce heart failure There is little evidence indicating that the stroke output is either consistently or significantly elevated The augmented cardiac output per minute and therefore the increased cardiac work per minute is in itself incapable of producing cardiac hypertrophy or cardiac failure as long as the work of the heart *per beat* is not greater [107]

There is however, evidence suggesting that the heart in hyperthyroidism is inefficient in its adaptation to an increased strain The hyperthyroid heart at rest is utilizing its reserves in a manner which resembles that of the normal heart performing heavy work Plummer and Boothby[85] and Briard and his associates[17] demonstrated that patients with hyperthyroidism were inefficient in converting potential energy into motion Bansi and Groscurth[4] found that the cardiac output, the oxygen consumption and the blood pressure during and after work were all increased in hyperthyroid patients to a relatively much greater extent than in normal individuals performing the same work Boothby and Rynearson[14] observed a greater augmentation in the cardiac output in patients with Graves disease than in normal subjects following similar increases in oxygen consumption caused by work

These varied observations, as well as a consideration of the circulatory changes already mentioned, suggest not only that the hyperthyroid heart is under strain to provide an adequate blood supply for the exaggerated oxygen demands of the tissues, but also that the adjustments employed are wasteful in their provision and utilization of this increased oxygen supply The heart muscle itself becomes especially sensitive to any deficiency in oxygen supply, partly because of its own in

creased metabolism and partly because it is constantly performing an excessive amount of work Although it is possible for the normal heart with rare exceptions to meet the added strains of hyperthyroidism this adjustment becomes more and more difficult if the heart is already impaired and enlarged by preexisting disease or if cardiac function becomes diseased as the result of progressive coronary deficiency in later years Cardiac hypertrophy due to rheumatic heart disease or hypertension or other cause increases the myocardial need for oxygen while coronary artery disease diminishes the supply in either circumstance the hyperthyroid heart already suffering from low oxygen reserve is especially vulnerable In summary it appears that the circulatory adjustments to the increased metabolism of Graves disease impose a heavy burden on the heart but a burden which is likely to produce congestive heart failure only when the heart is already vulnerable or becomes vulnerable because of associated independent disease

Mechanism of Atrial Fibrillation in Hyperthyroidism

The mechanism by which hyperthyroidism or its altered circulatory dynamics may cause or predispose to atrial fibrillation is unknown The high incidence of atrial fibrillation especially of the paroxysmal type is a distinctive feature in hyperthyroidism The frequency and transiency with which it appears shortly after thyroidectomy and the frequency with which preoperative transient or permanent atrial fibrillation is cured by thyroidectomy attest to more than an accidental relationship between hyperthyroidism and atrial fibrillation These observations may denote that the thyroid hormone represents a direct toxic cause of atrial fibrillation in susceptible individuals In hyperthyroid animals the oxygen consumption of cardiac tissue is greatly increased especially that of the atria [10] The excitability of the atria in hyperthyroidism has been related to this increase in oxygen consumption

It is also possible that the atrial fibrillation results from the augmented venous return to the heart with its prolonged exaggerated stimulation of the atrial muscle about the entrance of the great veins where an irritable focus may be induced Excessive vagal tonus has been credited with an important role in causing atrial fibrillation on the basis of experimental production of this arrhythmia by vagal stimulation in cats and its production in hyperthyroid patients by the administration of Mecholyl [79] Acetylcholine likewise favored the induction and maintenance of experimental atrial fibrillation whereas potassium chloride restored the fibrillation to sinus rhythm[17] However as a rule atrial fibrillation is found only in hyperthyroid patients in the older age groups and with associated cardiac disease This suggests that the latter may be the basic cause of the atrial fibrillation and that the hyperthyroidism merely increases its occurrence or hastens its development When the associated cardiac disease is sufficient in itself to cause atrial fibrillation thyroidectomy does not cure this arrhythmia

PATHOLOGY OF THE HEART IN GRAVES DISEASE

There are no constant or characteristic morphologic changes in the heart which might be attributed to hyperthyroidism Infiltrations of lymphocytes and histiocytes as well as areas of myocardial necrosis and extensive interstitial fibrosis have been reported [30, 35, 81] but careful controlled histologic studies have failed to substantiate these findings [88, 104] Likewise I have been unable to find pathologic evidence of characteristic cardiac changes due to hyperthyroidism in a postmortem study of more than 35 hearts in patients with this disease Necrosis fibrosis and reactive cellular infiltration observed in some hearts could be explained by the ischemic effects of associated coronary atherosclerosis

It is well to remember that the absence of distinctive morphologic changes in the hearts of hyperthyroid individuals does not exclude the possibility that hyperthyroidism produces important or distinctive metabolic changes which alter the function of the heart muscle fibers The evidence of glycogen depletion in the heart muscle in experimental hyperthyroidism has been noted

Size of the Heart

Postmortem studies almost uniformly disclose a high incidence of cardiac hypertrophy in Graves disease Willius and his associates[108] observed cardiac hypertrophy in 16 of 21 cases Kepler and Barnes[5] in 42 of 86 cases and Parkinson and Cookson[83] in 22 of 43 making a combined average of about 50 per cent of hypertrophied hearts

In a study of 27 autopsied cases [35] we found that 14 of the 27 hearts were hypertrophied, as determined by comparison with figures for normal heart weight relative to body weight However we observed that 12 of the 14 hypertrophied hearts were those of persons in whom the hyperthyroidism was complicated by hypertension severe coronary narrowing and/or atrial fibrillation Six of these 12 hypertrophied hearts were those of patients who had suffered from congestive heart failure The most extreme hypertrophy in the series was found in those hearts in which congestive failure had been present We concluded that cardiac hypertrophy is usually absent or of minimal degree in uncomplicated cases of Graves disease However, eventually cardiac enlargement and hypertrophy developed in about half the cases which come to autopsy in a general hospital because of complicating heart disease or hypertension Cardiac hypertrophy is found in those cases of hyperthyroidism in which there is also thyroid heart disease i e in which established atrial fibrillation or cardiac failure coexists

The absence of cardiac hypertrophy in uncomplicated hyperthyroidism may be related to the finding that the stroke output and therefore the diastolic tension are usually normal When cardiac hypertrophy occurs, it is the consequence of hypertension or associated valvular disease, most strikingly, it appears with progressive myocardial failure

CLINICAL FEATURES OF THE HEART IN HYPERTHYROIDISM

Many of the symptoms and signs referable to the heart and circulation are essential features of uncomplicated Graves' disease their presence does not warrant a diagnosis of thyroid heart disease Arbitrarily one may speak of thyroid heart disease when in addition to hyperthyroidism there is also persistent atrial fibrillation, distinct cardiac enlargement or congestive heart failure

SYMPTOMS

Palpitation is one of the commonest subjective symptoms referable to the heart in Graves disease As a rule it occurs independently of heart disease and is the consequence of rapid and forceful heart action as well as of hypersensitivity of the autonomic and central nervous system Palpitation may vary in severity from an uncomfortable awareness of the heart beat to an intense and sometimes terrifying pounding It may be present when the patient is at rest, especially when lying on his left side, but more often it appears or becomes accentuated with emotion and exertion or after a meal

Another type of palpitation occurs in paroxysms and is due to transient episodes of atrial fibrillation or, rarely, of flutter [53] It may be associated with faintness, weakness or precordial distress When these attacks of atrial fibrillation are accompanied by very rapid ventricular rates, the local distress is sometimes overshadowed by breathlessness Extreme weakness may follow subsidence of such an episode Occasionally a severe attack of paroxysmal atrial fibrillation may precipitate transient pulmonary edema or chronic congestive heart failure As a rule, however, these transient paroxysms of irregular heart action come and go and the patient learns to tolerate them

Similarly, *permanent* atrial fibrillation may provoke the subjective sensation of palpitation with or without an awareness of an irregular heartbeat, or it may be accompanied by more serious symptoms of congestive heart failure On the other hand, many patients with atrial fibrillation, transient or permanent, are unaware of the irregularity

Breathlessness is also a common symptom but its character and pathogenesis are distinctive from those of classic cardiac dyspnea It is often experienced on exertion and is associated with easy fatigability The combination reminds one of similar symptoms observed in neurocirculatory asthenia or cardiac neuroses In some of these cases the breathlessness occurs predominantly at rest and is the sighing type seen in psychoneurotic individuals

On the other hand, the dyspnea may be due to an actual disturbance in circulation or in pulmonary ventilation The oxygen consumption and cardiac output in hyperthyroid patients during and after work are increased much more than in normal persons performing the same exertion [4] The vital capacity has been found to be below normal in hyperthyroidism [■] The residual air and functional residual capacity were found to be increased [■] Because of these findings, the dyspnea has been explained as being due to increased pulmonary ventilation necessitated by coincident augmented oxygen consumption and decreased vital capacity [■]

But the dyspnea of uncomplicated hyperthyroidism, unlike that of heart failure, is not associated with evidence of pulmonary congestion, in fact the rate of blood flow through the lungs is accelerated and not delayed Therefore it appears improbable that the dyspnea is due to any circulatory abnormality It seems more likely that the respiratory distress in uncomplicated hyperthyroidism is induced by the easier fatigability of the muscles of respiration rather than by any intrinsic pulmonary disturbance The fatigability of the respiratory muscles may be the result of the increased work needed for the augmented oxygen supply or of an actual respiratory muscular weakness which is part of a general disturbance in creatine metabolism often present in hyperthyroidism [57] Dyspnea occurs more readily when the patient lives in an atmosphere of low oxygen pressure which interferes with his high oxygen requirement In fact dyspnea on exertion (occurring in 56 per cent of 140 cases) was described as the commonest symptom of hyperthyroidism in patients residing at the high altitude of Denver where the atmospheric pressure is low [18]

Finally, true cardiac dyspnea may become a prominent symptom as a result of the development of pulmonary congestion due to heart failure In such cases all of the features of cardiac dyspnea are present and there are often rales at the bases of the lungs while the circulation time although not prolonged is delayed in comparison with the rapid circulation time of uncomplicated hyperthyroidism

Precordial pain is an occasional symptom of hyperthyroidism It may represent only a mild discomfort associated with tachycardia and awareness of the heartbeat There may be a sticking type of pain in the region of the cardiac apex, such as occurs in many women with hypersensitive nervous systems On the other hand more intense precordial pain may accompany a paroxysm of atrial fibrillation with very rapid ventricular rate Occasionally such an episode may simulate an attack of acute myocardial infarction

In a small percentage of cases angina pectoris characterized by a compressing retrosternal and precordial pain with typical radiations and induced by effort and excitement may be associated with hyperthyroidism [58] Since this is seen most commonly in the older age groups it is probable that the angina pectoris results from concomitant severe coronary artery disease However, Lev and Hamburger[59] reported that the angina pectoris disappeared following subtotal thyroidectomy This suggests that the hyperthyroidism was at least a contributory factor in causing the pain perhaps by increasing the oxygen requirements of a myocardium already deficient in blood supply

OBJECTIVE MANIFESTATIONS

We are concerned here primarily with cardiac and other circulatory manifestations of hyperthyroidism but the predominant signs of this disease are usually outside the heart The latter include the characteristic stare, the warm moist and often ruddy skin the enlarged thyroid gland and the tremor In cases of thyroid heart disease many of these classic signs of hyperthyroidism are often obscure or may be overshadowed by the cardiac manifestations In particular exophthalmos is usually absent and the thyroid gland is not noticeably enlarged [44] Cases of cardiac disease or congestive heart failure with hyperthyroidism in which the classic signs of the latter seem to be absent or are easily overlooked are sometimes described under the heading of "masked hyperthyroidism" [60]

The Heart

Examination often discloses a broad striking precordial pulsation which is easily visible as well as palpable The apical thrust is often sharp and snapping These pulsations correspond to a steep rapid ascent of the ventricular contraction curve The strong pulsations may suggest the presence of cardiac hypertrophy but usually neither the position of the apical impulse nor percussion of cardiac dullness reveals any evidence of cardiac enlargement in uncomplicated cases

The *heart sounds* are loud and are distinguished especially by the first sound at the apex which is sharp and snapping often simulating the sharp first sound of mitral stenosis A systolic murmur is common and is usually most audible over the pulmonic area From time to time the sharp first apical sound in hyperthyroidism is associated with a distinct presystolic murmur under which circumstance the similarity to mitral stenosis presents a problem in differential diagnosis In my experience the association of rheumatic mitral stenosis with hyperthyroidism has been more common than is generally stated

Heart and Pulse Rate

As a rule, the pulse rate in Graves disease is between 90 and 120 per minute, but wider variations are encountered While the pulse rate in hyperthyroidism is abnormally increased by activity and emotional excitement, it also remains elevated when the patient is apparently calm and at rest Boas[12] has observed with the aid of the cardiotachometer that relatively little slowing of the heart rate occurs during sleep in contrast with the striking slowing of the tachycardia in psychoneurotic individuals

Pulse rates of 180 to 200 or more are sometimes observed in hyperthyroid patients either because of an extremely elevated metabolic rate, because of a paroxysm of atrial fibrillation or most commonly during a thyroid crisis or thyroid 'storm' following thyroidectomy

The pulse in hyperthyroidism is not only rapid, but often presents the full steep ascent and sharp rapid drop characteristic of the Corrigan or water hammer pulse found in aortic insufficiency Correspondingly, there may also be striking visible pulsations of the vessels of the neck These pulse characteristics result from the rapid discharge of blood from the heart into a dilated relaxed vascular bed

Atrial Fibrillation and Other Arrhythmias

In more than 75 per cent of the cases there is regular sinus rhythm at all times even when the heart rate is very rapid, but atrial fibrillation in paroxysmal or persistent form occurs with sufficient frequency to be considered a characteristic and diagnostic feature of hyperthyroidism Ernstene[8] noted atrial fibrillation at some time in about 21 per cent of 1000 cases but less than half of these were observed preoperatively Permanent atrial fibrillation occurred twice as often in this group as the paroxysmal variety Atrial fibrillation was recorded in 19 per cent of 279 cases of thyrotoxicosis studied by Jervell[33] mostly in the older age groups Hurxthal[47] encountered *established atrial fibrillation* in 5 8 per cent of 7363 patients operated on for hyperthyroidism, in terms of the thyrocardiac group this arrhythmia occurred in about 90 per cent of the cases More than 10 per cent of the total group of hyperthyroid patients had experienced *transient* atrial fibrillation before or after operation

Whereas *permanent* atrial fibrillation may be asociated with a variety of cardiac diseases especially rheumatic mitral stenosis and advanced coronary atherosclerosis, *paroxysmal* atrial fibrillation is highly suggestive of the presence of hyperthyroidism Temporary atrial fibrillation may appear for the first time or recur immediately following thyroidectomy, in either circumstance it usually disappears spontaneously after a few days or weeks Ernstene[28] observed that following thyroidectomy recurrent paroxysmal atrial fibrillation invariably reverted spontaneously to normal sinus rhythm if the patient survived On the other hand, thyroidectomy resulted in the spontaneous reestablishment of sinus rhythm in one third of the cases of established atrial fibrillation, of the remainder, a high percentage of restoration of sinus rhythm was effected by the administration of quinidine

Atrial fibrillation is associated predominantly with hyperthyroidism in the older age group Seventy five per cent of the cases of atrial fibrillation in Ernstene's[8] series occurred in persons above the age of 45 The severity of the hyperthyroidism does not appear to be a determining factor, for atrial fibrillation is uncommon in young persons with Graves' disease, even when the basal metabolic rate is extremely elevated When atrial fibrillation is encountered in patients under the age of 35 it is almost invariably paroxysmal Organic heart disease is frequent in cases of hyperthyroidism with atrial fibrillation, especially of the permanent variety More than half of Ernstene's patients with atrial fibrillation presented evidence of associated coronary, hypertensive or rheumatic heart disease Apparently, underlying cardiac disease is an important predisposing factor in the development of atrial fibrillation even though hyperthyroidism appears to be the trigger mechanism responsible for its appearance Finally, there is evidence that atrial fibrillation increases in frequency with the duration of the hyperthyroidism[108]

Other arrhythmias are extremely uncommon Premature beats occur occasionally but are not characteristic of hyperthyroidism *Rarely*, atrial flutter, paroxysmal atrial tachycardia or heart block is observed Davis and Smith[3] described 6 cases of complete heart block in hyperthyroidism due to acute infections or digitalis Unlike atrial fibrillation, these arrhythmias are not influenced by thyroidectomy

Blood Pressure and Pulse Pressure

The systolic blood pressure may be normal but more often it is at the upper limit of nor

mal or moderately elevated On the other hand the diastolic pressure is almost always normal unless there is an associated essential hypertension Occasionally the diastolic pressure is below normal Consequently the pulse pressure is usually elevated In fact an increased pulse pressure due to systolic hypertension is sometimes the clue to the discovery of hyperthyroidism But of course these findings are by no means limited to hyperthyroidism Occasionally an extremely wide pulse pressure resembling that of aortic insufficiency is associated with other dynamic changes characteristic of the latter disease namely prominent carotid pulsations Corrigan pulse pistol shot in the femoral arteries and capillary pulse

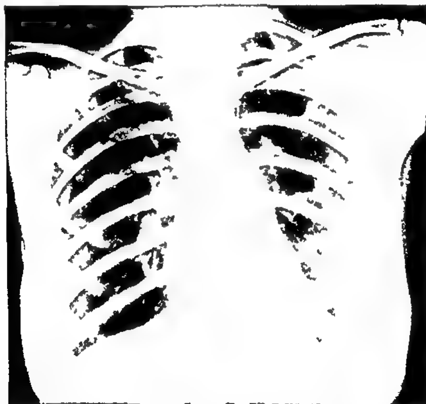


Fig 152 Heart in hyperthyroidism Pulmonary artery segment elongated and convex

The Circulation Time and Venous Pressure

In uncomplicated hyperthyroidism the velocity of blood flow is distinctly increased (p 1002) In my experience both the arm to-lung time determined with the aid of ether (p 215) and the lung to-tongue time (p 214) are significantly diminished but the greater reduction in circulation time appears to involve the segment from the antecubital vein to the pulmonary capillaries The arm to-lung time in such cases is usually between 3 and 4 seconds when the arm to-tongue time is between 8 and 10 seconds

The circulation time may remain rapid or within normal limits even when there are distinct clinical features of congestive heart failure and the venous pressure is elevated In such circumstances the circulation time may not be quite as abbreviated as in uncomplicated hyperthyroidism but usually it averages 10 to 15 seconds which is within the normal range of healthy persons This combination of congestive heart failure with a normal or rapid circulation time is distinctive of hyperthyroidism although it may also be observed in heart failure associated with vitamin B deficiency with fever, with severe cor pulmonale or with severe anemia

The venous pressure is usually normal in cases of uncomplicated hyperthyroidism When right as well as left sided heart failure develops the venous pressure becomes elevated

Roentgenologic Examination of the Heart

In uncomplicated hyperthyroidism roentgenologic examination of the heart discloses either no significant abnormality or a prominent pulmonary artery with increased pulsations (Fig 152) The sharp pulsations may extend to the remaining contours of the heart shadow [11] The prominence and accentuated pulsation of the pulmonary artery probably result from the augmented and accelerated blood flow which dilates that vessel The active pulsation of the cardiac borders resembles that seen fluoroscopically in cases of aortic insufficiency but in the latter it is the aorta which is prominent and pulsating vigorously The prominence of the pulmonary artery may result in straightening of the left border such as accompanies mitral stenosis But examination in the oblique positions fails to reveal the enlargement of the left atrium seen in mitral stenosis however both atria may become enlarged if congestive heart failure complicates hyperthyroidism

In uncomplicated cases there is no distinctive enlargement of the cardiac chambers Most observers however have described enlargement of the heart as determined roentgenologically in 25 to 45 per cent of their cases [8, 35, 66] The character of the cardiac enlargement observed is variable and in my opinion is determined by associated cardiovascular disease such as hypertension severe coronary artery disease or rheumatic heart disease When congestive heart failure is well established the heart is usually enlarged to the right and the left and the cardiac silhouette assumes a globular appearance

Electrocardiographic Examination

The electrocardiogram discloses no distinctive features except for the usual nonspecific sinus tachycardia or the occasional atrial fibrillation The former belief that the T waves become elevated in hyperthyroidism in contrast to the characteristically low T waves in myxedema has not been substantiated [9] Parkinson and Cookson[68] noted an elevated P wave (more than 3 mm) in over one third of their cases In my experience, a distinctive elevation of the P wave usually occurred when there was associated mitral stenosis and in some cases of heart failure Occasionally I have observed abnormalities of the QRS complex the RST segment or the T wave which however could reasonably be attributed to associated myocardial damage caused by coronary disease or to the effects of digitalis

Development of Congestive Heart Failure

The most serious consequence of hyperthyroidism is the development of congestive heart failure Congestive heart failure like atrial fibrillation, develops most frequently in older age groups and is rare under the age of 40[1], it occurs more often with associated hypertension coronary atherosclerotic or rheumatic heart disease than in their absence[12], it is more likely to develop the longer the duration of the hyperthyroidism, but is not distinctly related to its severity Andrus[1] encountered congestive heart failure in 18 5 per cent of 200 cases of hyperthyroidism In only 9 cases did symptoms of failure develop before the age of 40 and in 7 of the 9 there was evidence of coexisting heart disease Five of the 7 patients were found to have mitral stenosis when the basal metabolic rate was restored to normal, 1 had syphilitic heart disease, and in 1 case Aschoff bodies were found in the heart at postmortem examination Ernstene[21] reported congestive heart failure in 25 per cent of those of his cases of hyperthyroidism which were combined with various forms of heart disease, but no instances of congestive failure in 795 cases of hyperthyroidism without evidence of associated organic heart disease

Congestive heart failure usually develops after a period of established atrial fibrillation (p 1006) Hurxthal[47] noted that of 431 cases with established atrial fibrillation 55 7 per cent showed congestive heart failure But in his entire series of over 7000 cases the incidence of congestive heart failure was only 3 7 per cent The incidence of congestive heart failure in hyperthyroidism appears to be diminishing because of earlier recognition and treatment of hyperthyroidism

THE DIAGNOSIS OF THYROCARDIAC DISEASE

Diagnosis involves the recognition of both the hyperthyroidism and the cardiac complication One must recognize the presence of cardiac dysfunction in the patient with known hyperthyroidism and conversely, one must also recognize hyperthyroidism in the patient known to have atrial fibrillation and/or heart failure The diagnosis is simplest in cases in which there is a known history of hyperthyroidism or the characteristic stare and eye signs the tachycardia the warm moist skin,

the tremor the enlarged thyroid gland intolerance to heat, excessive perspiration loss of weight despite good appetite nervousness tendency to diarrhea and an elevated basal metabolic rate unexplainable by the degree of heart failure present In such cases of unmistakable Graves disease we may speak of thyroid heart disease if there is al[illegible] frequent paroxysmal or persistent atrial fibrillation unquestionable cardiac enlargement as revealed by roentgenologic examination or distinct evidences of congestive heart failure

In many cases one may discover an independent form of heart disease which could account for the atrial fibrillation cardiac enlargement or heart failure But even in cases with independent heart disease it is important to discover the associated hyperthyroidism without which the organic heart disease might not have produced clinical symptoms For in the presence of organic heart disease the alleviation of the hyperthyroidism usually causes a reversal of most or all of the important cardiac disabilities

A greater problem arises in those cases in which the predominant manifestations are cardiac and the presence and importance of the hyperthyroidism are discovered only secondarily (masked hyperthyroidism) Such discovery will occur if the possibility of hyperthyroidism is considered in all cases in which atrial fibrillation cardiac enlargement or heart failure of uncertain etiology [illegible] encountered Often in thyrocardiac patients the thyroid gland is small and there is no exophthalmos but there are usually a slight stare warm moist skin tachycardia a high pulse pressure and a history of weight loss without anorexia A search for an associated hyperthyroidism should be considered under the following circumstances

1 Paroxysmal or persistent atrial fibrillation or flutter of undetermined etiology especially if the rapid ventricular rate cannot be slowed by digitalis

2 Heart failure without apparent cause or heart failure which does not respond to digitalis and other appropriate treatment

3 Heart disease with unexplained tachycardia or tachycardia which persists despite treatment of heart failure or atrial fibrillation

4 Presence of congestiv[illegible] heart failure with out significant fever anemia or serious vitamin B_1 deficiency in which the circulation time is within the normal range

5 High systolic pressure out of proportion to diastolic pressure not explainable by other causes

Objective Tests of Hyperthyroidism

In any of the above groups adequate evidence of hyperthyroidism may be forthcoming as soon as the possibility is considered However in the presence of heart failure, it may be difficult to evaluate an elevated basal metabolism In such cases the diagnosis of hyperthyroidism can be confirmed by other objective tests

The most reliable objective tests[9, 8] of hyperthyroidism involve (1) the determination of the serum precipitable iodine (SPI) also termed protein bound iodine (PBI) and (2) the response to the administration of a tracer dose of radioactive iodine (I^{131})

Determination of the SPI involves a relatively elaborate chemical procedure[84, 6] but [illegible] probably the most reliable objective test of hyperthyroidism[84, 99] When the test is carefully performed the SPI is between 4 and 8 micrograms per 100 cc of serum in normal individuals and above 8 micrograms per 100 cc in hyperthyroidism False high values may result during pregnancy and after the administration of organic compounds of iodine e g after intravenous pyleography or after cholecystography or the diagnostic use of Lipiodol [illegible] There is evidence that SPI is increased also by the ingestion of Lugol s solution or potassium iodide[23] But it has been reported that the thyroxin fraction of the SPI as determined by butanol extraction [illegible] not elevated by the previous administration of Lugol s solution or other inorganic iodides[66] On the other hand the level of SPI may be falsely lowered in patients with congestive heart failure after intramuscular injections of Mercuhydrin[75]

Response to Tracer Dose of I^{131} The diagnosis of hyperthyroidism may also be made after the oral administration of a tracer dose of 25 to 100 microcuries of radioactive iodine (I^{131}) and determination of one of the following (1) the excretion of radioactive iodine in the urine during the subsequent 24 hours[50, 31] (2) the serum precipitable (protein bound) *radioiodine* in the blood after 48 or 72 hours[95, 103] (3) the radioiodine uptake by the thyroid gland after 4 or after 24 hours[105, 39, [illegible], 103] or (4) the thyroidal and renal plasma I^{131} clearance[10] Inorganic iodides must be withheld at least [illegible] weeks before iodine tracer studies because they diminish the radioiodine

uptake by the thyroid gland Similarly, 2 or 3 weeks should elapse after thiouracil therapy before radioiodine studies are made

The determination of the serum precipitable *radioiodine* after 72 hours has been found to be most useful for the diagnosis of hyper thyroidism [78] [81] If a 4 cc sample of serum or blood contains less than 0 27 per cent of the administered dose per liter of plasma, no further study is made and the patient is regarded as euthyroid If the value is 0 27 per cent or more of the administered dose per liter the *serum precipitable* I^{131} is determined as distinguished from the total I^{131}, which includes both inorganic I^{131} and I^{131} bound to protein The latter is precipitated by trichloracetic acid and determined separately

Hyperthyroidism is associated with a serum precipitable I^{131} exceeding 0 27 per cent of the administered dose per liter of plasma [81] According to Paley et al [82] hyperthyroidism is associated with a serum precipitable radio active I^{131} which exceeds 0 6 per cent per liter of the administered dose of I^{131}, as compared with the 0 27 per cent used as the critical level by Newburger et al [81] and 0 4 per cent of the dose per liter used by Wayne [103] Furthermore Paley et al [8] found the serum precipitable (protein bound) I^{131} determination less reliable as a test of hyperthyroidism than the thyroidal clearance of I^{131} in all their cases The serum precipitable I^{131} is frequently mislead ing in patients who have been treated with I^{131} since it may suggest persistent hypothyroidism in patients who have been rendered euthyroid by the treatment [8] [96] Despite the greater accuracy of the thyroidal clearance of I^{131} as an index of hyperthyroidism it is relatively cumbersome and requires an intravenous injection of the tracer material

The *thyroid uptake* of radioiodine in hyper thyroid patients after 24 hours exceeds 50 per cent of the administered dose, but many hyperthyroid as well as euthyroid patients have uptakes between 42 and 69 per cent [26] [81] [82] According to Greer and Smith[41] and Werner and Spooner [106] the differentiation between euthyroidism and hyperthyroidism in patients with equivocal radioiodine uptakes can be made by repeating the test after treatment with thyroid extract or triiodothyronine The latter substances sharply reduce radioiodine (I^{131}) uptake in euthyroid but not in hyper thyroid patients

The *24 hour urinary excretion* is usually less than 20 per cent of the administered dose in patients with hyperthyroidism (normal 30 to 60 per cent), but there are difficulties in obtaining complete 24 hour urine collections and false low values may result from marked oliguria in congestive heart failure

The value of these objective tests is indicated by the discovery of 8 cases of marked hyperthyroidism in a group of 55 patients with atrial fibrillation in whom hyperthyroidism was not previously suspected [■] The atrial fibrillation had been attributed to rheumatic coronary or hypertensive heart disease The accuracy of the diagnosis of hyperthyroidism appeared to be substantiated by reversion of the atrial fibrillation to sinus rhythm in 6 of 7 patients who were treated with radioiodine At the same time there was a distinct clinical improvement in their cardiac status The sinus rhythm was restored in four to nine weeks after treatment

Despite the usual accuracy of these objective tests of hyperthyroidism I have occasionally found it necessary to do a therapeutic test when there was a discrepancy between the clinical findings and the objective tests or between individual objective tests The administration of 10 to 30 minims of Lugol s solution daily for two or three weeks may confirm a diagnosis of hyperthyroidism if there is a good clinical response but in my experience this has often given equivocal results I have found it more satisfactory to give propyl thiouracil or Tapazole (infra) for six to ten weeks In cases of hyperthyroidism there is usually an excellent clinical result, and in thyrocardiac patients previously refractory heart failure is readily controlled

The differential diagnosis of hyperthyroidism is not pertinent to this volume From the cardiac point of view it may be necessary to differentiate hyperthyroidism from mitral stenosis because of the presence in both of a sharp first sound a systolic murmur and a prominent pulmonary artery However, this is not an important problem because the diagnosis of hyperthyroidism should be made on other criteria On the other hand mitral stenosis may be diagnosed and hyperthyroidism overlooked when there is a characteristic apical diastolic murmur and thrill especially in association with left atrial enlargement The presence of mitral stenosis does not exclude an associated hyperthyroidism nor conversely

TREATMENT

The treatment of thyroid heart disease is primarily *prophylaxis* Early recognition of uncomplicated hyperthyroidism and its prompt control will prevent the development of cardiac complications due to the hyperthyroid element

When atrial fibrillation or congestive heart failure is already present as well as hyperthyroidism it must be clearly recognized that the elimination of the hyperthyroidism should be the primary objective of the therapeutic attack Limitation of activity the restriction of salt and fluids, digitalization and the use of diuretics and other therapeutic measures for heart failure are all appropriate But all of these measures may be ineffective or of only limited value until the hyperthyroidism is corrected Therefore, unnecessary procrastination in an effort to control either the atrial fibrillation or the heart failure before undertaking treatment of the hyperthyroidism may be not only wasteful but dangerous Occasionally when the thyrocardiac patient is seen with atrial fibrillation and very rapid ventricular rates digitalization should be effected quickly to obtain the maximum possible slowing without toxicity Then the hyperthyroidism is treated without undue delay It is rarely desirable or necessary to administer quinidine in an attempt to restore sinus rhythm before treatment of the hyperthyroidism Sinus rhythm usually occurs spontaneously within a few weeks after the hyperthyroidism is eliminated But quinidine may be administered if the arrhythmia persists for more than a month after correction of the hyperthyroidism

Surgical Treatment

Although surgical treatment of thyrocardiac disease has given brilliant results this form of treatment is being continually superseded by the use of radioactive iodine Surgical control of the hyperthyroidism may be limited to those cases in which there is doubt as to the presence or absence of malignancy in the gland and to those cases with compression symptoms Subtotal thyroidectomy is regarded by some as the preferred treatment in the presence of a large nodular gland because of the slow response to antithyroid drugs or radioactive iodine and the larger dose required but these are not sufficiently important disadvantages to justify surgical treatment Surgery is preferred by some in the treatment of toxic goiter with solitary adenoma because of the purportedly high incidence of carcinoma in such solitary nodules[55] But the reported high incidence of carcinoma in resected solitary thyroid adenomata is at variance with the extremely infrequent appearance of thyroid carcinoma with metastases in cases studied clinically or by autopsy Radioiodine has been regarded as contraindicated and surgery preferred in the treatment of hyperthyroidism during pregnancy or lactation, in children and in uncomplicated hyperthyroidism in patients below the age of 40

Preoperatively the patient is treated with Tapazole 30 to 120 mg daily in three equal doses or propylthiouracil 300 to 600 mg daily, until the desired reduction in basal metabolism and clinical improvement are obtained[65, 67] Compound solution of iodine in doses of 10 to 20 minims daily is prescribed for ten to fourteen days to reduce vascularization of the gland before operation or iodinated thiouracil (Itrumil) may be given alone preoperatively A high caloric and vitamin intake is given Heart failure if present is treated as described elsewhere (Chapter 11) but operation is not delayed even if heart failure persists If haste is indicated the patient may be prepared with Lugol s solution alone for about two weeks, as before the use of the uracil drugs If the hyperthyroidism is not sufficiently controlled by these various therapeutic measures *corticotropin* (ACTH) may be administered for a few days preoperatively and continued through the stress period

At operation a subtotal thyroidectomy is performed[67] The importance of employing a skillful and experienced surgeon and of avoiding a prolonged operative procedure hemorrhage and other causes of shock, cannot be exaggerated It may be necessary occasionally to do the operation in two stages Endotracheal anesthesia using ethylene followed by ether has given satisfactory results[67]

Postoperatively, the patient should be placed in an oxygen tent If fluids are given parenterally they should consist of [illegible] per cent glucose in distilled water and should be administered very slowly to avoid pulmonary edema The basal metabolism rate should return to normal in two to four weeks If the patient was digitalized preoperatively, maintenance doses of digitalis are continued after operation until it is apparent that the hyper-

thyroidism has been eliminated By that time evidence of heart failure usually disappears or will respond to the appropriate therapeutic measures, and digitalis may be discontinued Atrial fibrillation almost always disappears with elimination of hyperthyroidism, although it may appear briefly postoperatively and disappear spontaneously If it persists for more than two weeks after operation it usually disappears after quinidinization (p 368) If this is ineffective the arrhythmia is probably due to independent cardiac disease and the patient should be digitalized to the desired point of slowing of the ventricular rate

[illegible][40] reported an operative mortality rate of 1 1 per cent in 181 thyrocardiacs which was about five times as high as for uncomplicated Graves disease Griswold and Keating[6] reported a series of 810 cases of hyperthyroidism with an operative mortality of 0 9 per cent among 103 thyrocardiacs as compared with 2 2 per cent for the noncardiac cases The operative mortality is now nearer 1 per cent for thyrocardiacs and only 0 2 per cent for uncomplicated hyperthyroidism since the use of the uracil preparations preoperatively There is a recurrence of hyperthyroidism in about 10 per cent of cases probably because of inadequate removal of thyroid tissue[6, 4] Myxedema due to excessive removal of tissue, tetany due to accidental removal of the parathyroid glands and hoarseness or respiratory distress due to injury of the recurrent laryngeal nerve are [illegible] postoperative [illegible]

Propylthiouracil and Tapazole (Methimazole)

[illegible]

[illegible]

[illegible]

longer period If the thyroid gland is large or if iodine has been given in the previous [illegible] weeks, the effect of the uracils is delayed Therapy may have to be continued for six months to a year or longer In the majority of cases, the improvement obtained persists when the drug is discontinued[7], in the others there is a return of symptoms within a few months

Initial control of hyperthyroidism may be obtained in 90 per cent of patients, but a remission is *maintained in only 40 to 60 per cent* after the thiouracil therapy is discontinued[21, 32, 37, 70, 40]

The chief toxic effect of the uracils is agranulocytosis, but this occurs much less frequently with propylthiouracil or Tapazole than with the other preparations Blood counts must be done at weekly intervals Prompt discontinuance of the drug, if granulocytopenia develops and the administration of penicillin almost always permit recovery from this complication Other less serious toxic effects include fever, rashes lymphadenopathy, joint pains nausea and vomiting[77] They usually disappear *promptly* after the drug is discontinued Prolonged uracil therapy may produce myxedema which may be disclosed by an elevated serum cholesterol before there is a significant reduction in the basal metabolic rate

Radioactive Iodine

Radioiodine (I^{131}) is now the preferred method of treatment of hyperthyroidism, particularly in thyrocardiac patients Patients with hyperthyroidism and a solitary nodule [illegible]

[illegible]

reserved only for patients beyond the age of 40 This risk is not important in thyrocardiac patients since they are usually well beyond the age of 40 Radioiodine therapy is contraindicated in pregnancy because the fetal thyroid can concentrate iodine after the third month during lactation it is contraindicated because the radioiodine may be secreted in the milk of lactating women

When radioactive iodine is given orally the iodine is taken up rapidly and selectively by the thyroid secreting cells of the thyroid gland There the contained radioactivity produces destructive effects similar to those of roentgen rays [illegible] Hertz and Roberts[45] and Chapman and Evans [9] showed that hyperthyroidism could be controlled with radioiodine as effectively as with subtotal thyroidectomy or the uracils I^{131} with a half life of eight days (or a biologic half life of six days to allow for excretion) is employed Dosage is given empirically with modifications according to the clinical estimate of the weight of the thyroid gland and the thyroid uptake of a tracer dose of radioiodine The normal gland weighs about 20 or 25 gm The thyroid gland in thyrocardiacs is usually only moderately enlarged (40 to 60 gm) Very large glands may weigh 100 to 200 gm or more The initial dose is usually 150 to 250 microcuries per gram of estimated thyroid weight [3, 65, 21, illegible] The usual effective dose is about 8 to 12 millicuries of I^{131} by mouth for a hyperthyroid patient with a gland estimated as weighing 40 to 60 gm , but there are considerable individual variations

Nelson et al [illegible] administered 150 to 250 microcuries per estimated gram of thyroid weight as the initial dose in cases of diffuse toxic goiter and 300 to 350 microcuries per gram of estimated thyroid weight in cases of nodular toxic goiter The average dose for remission averaged 11 millicuries for diffusely enlarged glands and 20 millicuries for nodular glands but there were large variations from these averages in individual cases Adequate dosage is usually given in one or two doses in about 75 per cent of hyperthyroid patients but three to ten doses may be necessary in the remaining patients before a remission is effected The initial dose is designed to undertreat slightly and a subsequent dose or doses are administered if there are residual clinical symptoms

An interval of at least eight weeks should elapse between doses since 99 per cent of the radioactivity is dissipated in this period Inorganic iodine must not be given in the eight weeks prior to I^{131} because the gland may become saturated with the former and will not take up the radioiodine However three days or more after the therapeutic dose of I^{131} has been given compound solution of iodine is given for three weeks to obtain a rapid therapeutic effect until the radioiodine produces a more thorough and persistent result

Clinical improvement usually is observed in ten days to three weeks and the basal metabolism is reduced to normal in two to four months A mild and transient myxedema may occur and in 5–10 per cent a more severe and persistent one, requiring small doses of thyroid

In patients with thyrocardiac disease atrial fibrillation and cardiac failure usually disappear without further treatment If atrial fibrillation persists after the basal metabolism is reduced to normal it usually responds rapidly to quinidine even if it failed to respond prior to radioiodine therapy If not the patient should be digitalized Similarly heart failure responds satisfactorily to limitation of activity, digitalization, sodium restriction diuretics etc , even if it was refractory before the hyperthyroidism was controlled B complex should also be administered

In a study of approximately 600 hyperthyroid patients followed for at least six months after treatment with radioiodine hyperthyroidism was eliminated in all and there were no recurrences [illegible] The thyroid was diminished in size in all sometimes to normal Temporary hypothyroidism requiring thyroid therapy, developed in 14 per cent but only 1 per cent had apparently permanent myxedema The exophthalmos improved in most but unilateral exophthalmos developed in 4 patients McCullagh[69] observed only 2 failures and 8 recurrences in the treatment with I^{131} of 1235 patients with Graves disease Similar satisfactory results were reported by Bloomfield et al [11] in a series of 140 cases and by Balls et al [2] in a series of 228 cases

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Chapter 41

THE HEART AND CIRCULATION IN MYXEDEMA

Advanced myxedema is commonly associated with roentgenologic abnormalities in the cardiac silhouette and with electrocardiographic changes Furthermore there is a strong suspicion that myxedema predisposes to coronary atherosclerosis and its cardiac complications But the existence of a specific form of myxedema heart disease which leads to heart failure is unproven

Myxedema heart was first proposed as a clinical entity by Zondek[11] who described diffuse enlargement of the heart sluggish cardiac contraction and electrocardiographic abnormalities all of which were reversible upon treatment with thyroid substance These observations were confirmed without substantial change by many others[12, 25, 40] but there is disagreement as to the nature and significance of the observed abnormalities

The cardiac and circulatory changes to be noted are found only in cases of hypothyroidism in which the clinical picture of myxedema is fully developed These patients have not only a very low basal metabolic rate (usually below minus 25) but also cold dry, thickened and often edematous skin loss of hair and mental retardation The cardiac and circulatory alterations associated with myxedema are not observed in cases of hypothyroidism without myxedematous skin changes and mental retardation even when the basal metabolic rate is minus 20 or lower

The changes classified as "myxedema heart" are relatively rare since advanced myxedema is observed uncommonly The incidence of cardiac abnormalities among cases of myxedema is variously reported from occasional to almost 100 per cent According to Lerman, Clark and Means[5] myxedema heart as described by Zondek[5] occurred in 80 per cent of 48 adult cases of myxedema Fahr[12] noted not only cardiac changes but evidences of cardiac failure in 75 per cent of 17 severe and moderately severe cases of myxedema McGavack and his associates[20] also reported severe cardiac disturbances in 79 per cent of 24 cases of myxedema The so-called myxedema heart is observed with infantile as well as adult forms of myxedema[3] Mussio-Fournier[35] observed the characteristic cardiac changes in 7 of 18 cases (38 per cent) of infantile myxedema Blumgart and associates[7] found no increase in the degree of atherosclerosis that might be attributed to myxedema induced by total thyroidectomy for heart failure after an average period of 7 4 years

Age and Sex

Myxedema and "myxedema heart are observed predominantly among women They occur at all ages but in adults especially after the age of 40

PATHOLOGY OF THE HEART

The scanty pathologic data thus far available provide insufficient evidence of a specific histologic cardiac lesion associated with myxedema Schultz[4] described an homogenous infiltration, staining blue with hematoxylin, but differing in staining properties from the myxedematous infiltration occurring in the skin Other non specific changes have also been noted, including necrosis or degeneration of muscle fibers and replacement fibrosis[32] The muscle may appear grossly edematous,[11] and in the hearts of thyroidectomized animals edema has actually been demonstrated by measurement of the water content[43]

Pericardial effusion, sometimes of considerable size (1000 cc), has been demonstrated clinically[11] in autopsied cases[5] and in experimental hypothyroidism[49] but not in myxedema induced by radioactive iodine (I[131]) therapy[22] There is no evidence of associated pericarditis, thus the effusion represents an hydropericardium

Dilatation and hypertrophy of the heart have been reported repeatedly, hypertrophy having been noted in 7 of the 20 autopsied

cases collected by the Clinical Society of London[39] However there is no convincing evidence of true cardiac hypertrophy in myxedema uncomplicated by independent cardiac disease A pseudohypertrophy possibly due to edema was noted grossly by Means[31]

It is generally believed that atherosclerosis develops earlier and with greater frequency and intensity in cases of myxedema than usual[4] and this has been related to altered lipid metabolism in myxedema notably the associated hypercholesterolemia (p 425)[27] Fishberg[15] reported advanced arteriosclerosis in a boy of 21 with thyroid deficiency and Willius[50] observed a myxedematous patient of 23 who succumbed to heart failure due to advanced coronary sclerosis and myocardial fibrosis proven at autopsy However these appear to be exceptional cases for myxedema may be associated with normal coronary arteries There is a surprising paucity of pathologic support for a belief so widely held namely that myxedema predisposes to coronary atherosclerosis A relationship between myxedema and coronary atherosclerosis is supported by a number of reports of the production of atherosclerosis in thyroidectomized animals[17] But the application of these experimental findings to human myxedema and coronary atherosclerosis can only be considered with reservations

PATHOLOGIC PHYSIOLOGY

Basal Metabolism and Oxygen Consumption

Myxedema is characterized by a *reduction in basal metabolism* i e a diminution in the oxygen consumption of the tissues As a rule there is a reduction of 20 to 40 per cent below normal Consequent to the diminished metabolism there is a sharp reduction in heat production In contrast to patients with hyperthyroidism who experience excessive heat production and uncomfortable sensitivity to warmth patients with myxedema are unpleasantly sensitive to cold because of a deficient production of heat

Peripheral Blood Flow

The peripheral blood flow was found to be diminished by Stewart and Evans[45] and by Abramson[1] Corresponding to the diminished blood flow the peripheral vascular channels are narrowed Ellis et al[11] found the peripheral resistance regularly increased in myxedema Thus Zondek Michael and Kaatz[53] found the capillaries of the nail bed extremely reduced in number and very narrow in caliber There is an approximate linear relationship between the basal metabolism and peripheral blood flow Instead of a normal blood flow to the skin of 3 to 4 per cent of the total cardiac output only 1 3 per cent of the cardiac output was allotted to the skin in patients with an average basal metabolic rate of minus 30[46] By contrast in patients with hyperthyroidism 6 per cent of the total cardiac output is apportioned to the skin

Venous Return and Minute Volume (Cardiac Output)

The diminished peripheral blood flow results in a *reduction of the venous return* to the heart and thus in turn is reflected by a *fall in the minute volume* (cardiac output)[18, 45, 17] Ellis et al[11] found the cardiac output in 5 patients with myxedema to be diminished to a greater degree than the diminution in oxygen consumption According to the observations of Stewart et al[45] the cardiac output in cases of myxedema averaged 1 17 liters per minute per square meter of body surface before treatment and 1 98 liters after adequate treatment with thyroid It is noteworthy that whereas the cardiac output was 60 per cent of normal the proportion supplying the skin was only 25 per cent of normal This indicates that there is a relatively greater reduction of the cardiac output going to the skin in myxedema than to other organs another example of the mechanism of heat conservation in this disease

The *arteriovenous difference* is increased in cases of myxedema[45, 11] owing to slowing of the peripheral blood stream which permits greater oxygen utilization by the tissues This reduces the load on the heart consequently the cardiac output and work of the heart in myxedema are diminished to a greater degree than is the oxygen consumption Since the efficiency of the heart is greater the less work it performs for a given amount of body metabolism, the heart in myxedema is more efficient than normally Briard and his associates[5] demonstrated a very efficient conversion of calories into kg meters of work as compared to the response of the heart in hyperthyroidism In fact 19 per cent less energy was utilized by myxedematous patients in walking than by normal subjects The mechanisms described for conserving heat probably account for the improved efficiency in myxedema In hyperthyroidism the cardiac output and work of the heart are increased even more

than the oxygen consumption, i e, cardiac efficiency is diminished, probably because of the energy wasted in the dissipation of excessive heat

Heart Rate

Bradycardia is a frequent finding in advanced myxedema The pulse rate frequently ranges between 50 and 70 in the absence of conduction disturbances The mechanism of the slow pulse rate is uncertain although it may represent a reverse of the Bainbridge reflex due to the slow and diminished venous return (contrast with hyperthyroidism p 1006)

Blood Pressure and Pulse Pressure

The blood pressure shows no constant or significant change

Velocity of Blood Flow Circulation Time Venous Pressure

The blood flow is significantly slowed in proportion to the degree of reduction in basal metabolism and the slowing of the peripheral blood flow [45, 50] The circulation time from arm to tongue is frequently between 20 and 30 seconds compared to a normal of between 9 and 16 seconds But Ellis et al [11] found the circulation time in myxedema (with magnesium sulfate) to be between 15 and 18 seconds

The *venous pressure* is usually normal [45] However, Mussio Fournier and his associates[36] reported an elevation in venous pressure in at least 6 of 12 cases of myxedema heart disease But these observers could find no relationship between the venous pressure as they determined it and the presence or absence of heart failure Careful determinations of the venous pressure should help to decide whether the serous effusions and edema are evidences of heart failure or of myxedema

Blood Volume

The *circulating blood volume* was found to be diminished by Thompson[47] and by Gibson and Harris [16] According to Ellis et al ,[11] the plasma volume is normal but the total blood volume is diminished due to a lowered hematocrit The radiosodium space is high suggesting an increase in the interstitial fluid space [1]

Vital Capacity

The *vital capacity* is significantly diminished[18] in spite of the absence of pulmonary congestion The vital capacity in myxedema is similar to that in hyperthyroidism whereas most of the circulatory disturbances in these two conditions provide distinct contrast The vital capacity in myxedema may be reduced by the frequently associated elevation of the diaphragm and occasionally by the presence of pleural effusions It should be noted that there is disagreement as to the vital capacity in myxedema, for Schnitker, van Raalte and Cutler[40] failed to observe a reduction in vital capacity in cases of hypothyroidism following thyroidectomy

CLINICAL FEATURES OF MYXEDEMA HEART

Subjective symptoms referable to the heart are relatively uncommon and consist of angina pectoris or complaints due to congestive heart failure

Objective findings are more frequent and more characteristic and include enlargement of the heart sluggish cardiac action electrocardiographic changes and signs suggesting congestive heart failure

Cardiac Enlargement

The heart is definitely enlarged in most cases of advanced myxedema The enlargement, which extends both to the left and the right, gives the cardiovascular silhouette a ham shaped configuration (Fig 153) There is a close resemblance to the roentgenologic appearance of pericardial effusion In 34 of 48 cases of myxedema, Lerman Clark and Means[-] observed cardiac enlargement as denoted by a transverse diameter which exceeded half the diameter of the chest by 1 cm or more, in 22 of these the transverse diameter of the heart exceeded half the diameter of the chest by 5 cm or more

Thyroid hormone specifically reduces the size of the heart (Fig 153), withdrawal of the thyroid is followed by enlargement to its previous size [8, 11] After three to four weeks of treatment there is a noticeable shrinkage of the cardiac shadow, but complete restoration to normal size may require continuous treatment for at least six weeks and sometimes for three to four months The rapid development and reversibility of the cardiac enlargement in myxedema suggest that there is no true hypertrophy of the myocardial fibers

The cause of the cardiac enlargement is uncertain The absence of specific pathologic changes in the heart has been discussed (p 1016) The enlargement may be due chiefly or partially to myxedematous infiltration or interstitial edema similar to that occurring in the skin and subcutaneous tissue

Enlargement of the cardiac silhouette has been attributed to an associated *pericardial effusion* rather than to dilatation or hypertrophy of the heart itself [41] In fact the similarity of the roentgenologic appearance of the heart in myxedema to that of pericardial effusion has already been noted (p 1018) Pericardial effusions of considerable size have been aspirated repeatedly during life [9, 14] and have been noted also at autopsy [illegible] The findings at postmortem examination are usually obscured by the effects of thyroid administered during life Furthermore pericardial aspiration has been performed in a relatively small number of cases, even when fluid is obtained it is not always sufficient to explain the degree of cardiac enlargement [20] But Kern et al [21] by means of pericardial taps in 4 successive cases provided strong evidence that pericardial effusion is a constant and major factor in the cardiac enlargement and other features of myxedema heart In the present state of knowledge it appears most probable that the enlargement is due partially to myxedematous infiltration or interstitial edema similar to that in the skin and that pericardial effusion may contribute in varying degree to enlargement of the cardiac silhouette

Pleural and peritoneal effusions may be associated with an effusion in the pericardium Among 25 cases of myxedema with pericardial effusion with data referable to other serous cavities there were associated pleural or peritoneal effusions or both in 13 [22]

Sluggish Cardiac Action

Physical and roentgenologic examination of the heart in myxedema discloses a sluggish action which contrasts with the dynamic hyperactivity of the heart in Graves disease

On physical examination it is usually difficult or impossible to feel a precordial pulsation or to localize the apical impulse The heart sounds are soft and distant

Fluoroscopic examination discloses sluggish cardiac contractions, wormlike in character and of minimal amplitude This is remarkable because of an associated bradycardia which usually consorts with strong cardiac pulsations The pulse is extremely small and the rate slowed to 50 to 70 per minute

Cardiac Failure

There is considerable disagreement as to the incidence of congestive heart failure in patients with myxedema It is questionable whether it ever occurs independently of associated intrinsic cardiac disease such as coronary atherosclerosis with myocardial infarcts According to Fahr [12] symptoms and signs of heart failure were present in 13 of 17 cases i e in 75 per cent and in 5 of them these manifestations were severe All of the patients presented dyspnea rales at the bases of the lungs and pitting edema Similarly McGavack and his associates[30] observed 24 patients with frank myxedema of whom 19 exhibited evidence of severe heart failure But other etiologic factors could not be excluded since 1 patient had syphilitic aortitis 13 had arteriosclerotic changes and 5 had hypertension On the other hand, many observers have never witnessed congestive heart failure in association with myxedema, or have been able to attribute it to independent etiologic forms

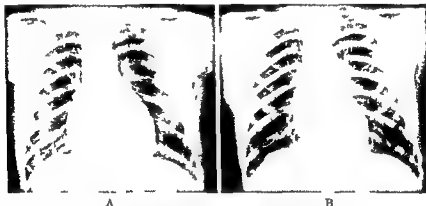


Fig 153 Heart in myxedema *A* Generalized enlargement of the heart when B M R was —50 per cent *B* After two months of treatment with thyroid hormone

of heart disease [51, 5] There are many reasons for concluding that the manifestations of myxedema which simulate those of myocardial insufficiency are actually unrelated to failure of the heart This does not contradict the occasional occurrence of true heart failure as a result of an associated independent cardiac disease

Angina Pectoris and Coronary Occlusion

The association of angina pectoris with myxedema was noted by Zondek,[52] and more recently was reviewed by Peel[38] The angina pectoris is probably due to severe coronary atherosclerosis Bartels and Bell[4] reported that among 59 patients beyond the age of 20 with spontaneous myxedema 15 presented clinical evidence of coronary artery disease The anemia sometimes found in myxedema may be a contributory factor Most frequently the angina pectoris appears only after the institution of thyroid therapy and the elevation of the basal metabolic rate as noted by Means, White and Krantz,[33] and by Christian[9] In these cases also it is probable that the angina pectoris was due to coronary atherosclerosis but myocardial anoxia sufficient to cause pain did not develop until the work of the heart was increased by thyroid therapy

A more obscure group is formed by the cases in which angina pectoris associated with myxedema is reported to have improved following treatment with thyroid Such cases have been documented by Laubry, Mussio-Fournier and Walzer[24] Beach[5] and by Beaumont and Robertson[6] A satisfactory explanation for the mechanism by which thyroid therapy could relieve angina pectoris has not been submitted The descriptions of the angina pectoris in the reported cases are quite meager and one may question whether these patients suffered from angina pectoris or from chest pain of non-cardiac origin In the case reported by Beaumont and Robertson the correlation between relief and thyroid therapy is not convincing, furthermore the reported electrocardiographic changes suggest that relief of the paroxysms followed the occurrence of myocardial infarction

Very few autopsy reports are available, but in those recorded in recent years coronary occlusion and myocardial infarction appear common In the single autopsied case described by Fahr[13] there was an atherosclerotic coronary occlusion with necrosis of the myocardium In the only 2 cases of Higgins[19] in which autopsies were obtained, old or recent coronary occlusion and myocardial infarction were present in both Similarly there was an acute coronary occlusion in the autopsied case reported by Means and Lerman[3] and in that reported by Smythe[41]

Electrocardiographic Changes

The electrocardiographic changes represent a cardinal feature of the myxedema heart as described by Zondek[52] These changes consist of (1) low voltage of all the complexes, but most frequently of T and P, (2) flattening or inversion of the T waves, (3) restoration of upright T wave and increased voltage of the ventricular complexes following thyroid therapy

The most constant feature is the flattening or inversion of the T waves, especially in leads I and II These may become upright following the administration of potassium salts[43] The P waves may also be almost flat or absent in one or more leads

The P R interval is frequently at the upper limit of normal and occasionally it is prolonged to as much as 0 4 second Partial heart block, which improved after thyroid therapy, was reported by Willius,[50] Fahr[12] and others In such cases the heart block has been attributed to myxedematous infiltration of the bundle of His or to increased vagal tone On the other hand an excessive P R interval may persist or become prolonged despite thyroid medication This usually denotes that the heart block is caused by independent cardiac disease (due to coronary atherosclerosis), for there are often associated intraventricular conduction disturbances and negative T waves which likewise persist despite specific therapy

Sometimes the QRS complex is notched widened and of low voltage in the absence of a prolonged P R interval This also suggests the presence of independent myocardial disease As a rule the QRS complex is more likely to remain unaltered in myxedema than the P or T waves The salient feature of the electrocardiographic changes due to myxedema is their correction by adequate and prolonged thyroid medication Within three weeks there is an increase in voltage the T waves if inverted become upright and the P waves reappear or become taller

The cause of the characteristic electrocardiographic abnormalities is uncertain but their rapid regression following thyroid therapy indicates a direct relationship to the

myxedema itself. Poor conductivity (i.e., increased electrical resistance) resulting from the thickened edematous skin[37] [illegible] is not the cause, since identical tracings are obtained by direct needle electrodes that pierce the skin[10] or are inserted into veins in the extremities.[35] The similarity to the electrocardiogram associated with pericardial effusion suggests that the changes observed with myxedema are actually due to a concomitant pericardial effusion.[41] But the association of a significant pericardial effusion in all cases of myxedema with typical electrocardiograms and the regular disappearance of the electrocardiographic abnormalities after pericardial paracentesis are unproven. The low voltage of the atrial and ventricular complexes may actually mirror weak action currents associated with the sluggish cardiac contraction in myxedema. A variety of other explanations[18] relating the electrocardiographic changes to vagotonia, low basal metabolism,[34] associated anemia, and myocardial anoxia have been offered without conclusive or consistent evidence. Studies of the T vector in the spatial vectorcardiogram in myxedema suggested that the observed alterations were due to altered cellular metabolism which retarded the process of repolarization in the involved muscle.[49]

DIAGNOSIS

The presence of myxedema should be recognized from the characteristic cold, dry, thickened skin, scanty hair and eyebrows, puffy eyelids, mental and physical sluggishness, constipation and intolerance to cold. In the cases associated with cardiac and circulatory changes the basal metabolic rate is usually between minus 25 and minus 35 per cent. The presence of "myxedema heart" is denoted by significant cardiac enlargement to the left and the right and by the low voltage and flattening and inversion of the T waves in the electrocardiogram in patients with the above mentioned evidences of myxedema. Diagnostic confirmation is obtained by the reduction in the size of the heart, the restoration of a normal electrocardiogram and other evidences of clinical improvement following thyroid therapy.

Occasionally, when other signs of myxedema are overlooked, the possibility of this condition should be considered when there is (1) unexplained cardiac enlargement, (2) clinical or roentgenologic evidence of pericardial effusion, (3) flattening or inversion of the T waves, or (4) diffuse anasarca without evidence of hypertension, rheumatic cardiovalvular disease or coronary atherosclerosis. The therapeutic effect of thyroid should be observed whenever there is doubt as to the possible myxedematous origin of these abnormalities.

TREATMENT

Thyroid substance or thyroxin is the specific treatment for myxedema with or without *cardiac and circulatory* abnormalities. The important point to remember is that the thyroid must be administered cautiously and in small dosage because of the danger of precipitating angina pectoris and, more seriously, heart failure, especially acute left ventricular failure.[illegible] Satisfactory initial doses range from 1/20 to 1 grain of thyroid substance daily. Ultimately stabilization can usually be attained by doses of 30 to 180 mg (½ grain to 3 grains) daily. This applies to preparations containing 0.2 per cent iodine according to U.S.P. standards. Since various preparations may differ in potency, the dosage should be adjusted accordingly.

As a rule it is safe to begin with 8 mg (⅛ grain) of thyroid daily and to increase it gradually by increments of 8 mg according to the clinical response. If possible the patient should be ambulant in order to observe the effect of activity. Four to eight weeks are usually required to obtain a satisfactory result. If angina pectoris develops, it may be necessary to maintain the patient at slightly hypothyroid levels. With satisfactory treatment there is a striking diminution in the size of the heart, increase in voltage of the ventricular complex in the electrocardiogram, more forceful cardiac activity, increase in the cardiac output and volume, heart rate and rate of circulation, as well as an elevation in the basal metabolic rate and a regression of serous effusion and other evidences of myxedema. Loss of weight and a fall in blood cholesterol are early objective signs of improvement.

Digitalis is of no benefit and is not indicated for the treatment of the cardiac and circulatory changes due to myxedema alone. Occasionally it may be difficult to distinguish whether some of the symptoms and signs represent congestive heart failure or the consequences of myxedema alone. In such cases

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As a rule it is safe to begin with 8 mg (⅛ grain) of thyroid daily and to increase it gradually by increments of 8 mg according to the clinical response If possible, the patient should be ambulant in order to observe the effect of activity Four to eight weeks are usually required to obtain a satisfactory result If angina pectoris develops it may be necessary to maintain the patient at slightly hypothyroid levels With satisfactory treatment there is a striking diminution in the size of the heart increase in voltage of the ventricular complex in the electrocardiogram more forceful cardiac activity increase in the cardiac output and volume heart rate and rate of circulation as well as an elevation in the basal metabolic rate and a regression of serous effusion and other evidences of myxedema Loss of weight and a fall in blood cholesterol are early objective signs of improvement

Digitalis is of no benefit and is not indicated for the treatment of the cardiac and circulatory changes due to myxedema alone Occasionally it may be difficult to distinguish whether some of the symptoms and signs represent congestive heart failure or the consequences of myxedema alone In such cases

the myxedema should first be controlled by thyroid administration After adequate treatment, it may be apparent that there are residual symptoms which must be interpreted as those of congestive heart failure, usually due to coronary atherosclerosis In such cases, digitalis and other measures directed toward the control of heart failure (Chapter 11) should be instituted

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Chapter 42

OTHER ENDOCRINE, METABOLIC AND NUTRITIONAL DISTURBANCES

THE PITUITARY

It is conceivable that the most important effects of the pituitary gland on the development of cardiovascular disease are still unknown. Through its influence on fat and protein metabolism it may be concerned with the pathologic lipid alterations in coronary atherosclerosis. Selye and his associates[10] have described the occurrence of renal arteriosclerosis and myocardial fibrosis following injections of anterior pituitary extracts in rats but these observations may not be transferable to human pathology. A relation of the anterior pituitary to edema has been suggested because of the occurrence of premenstrual edema[15] and of edema in the toxemia of pregnancy.[6] These may be adrenotrophic or gonadotrophic effects. More definite relationships to cardiovascular pathology are found in the specific diseases or syndromes resulting from hyperfunction or hypofunction of the anterior pituitary gland.

HYPERFUNCTION OF THE ANTERIOR PITUITARY ACROMEGALY

Acromegaly is characterized by enlargement of the skull, mandibles and the terminal parts, the adjacent soft tissues and in fact all the viscera. With respect to the heart the most impressive finding is a pronounced *cardiac hypertrophy* exceeding that to be anticipated from the generalized splanchnomegaly.[12, 14] The weight of the heart commonly exceeds 500 gm.[4] Occasionally the weight of the heart ranges approximately between 1000 and 1300 gm.[7, 4] Cronk[5] recently reported the presence of myocardial calcification and a heart weight of 950 gm. in a man with pituitary adenoma and acromegaly weighing 150 kg. A second finding which is stressed less often is the common occurrence of advanced atherosclerosis, notably coronary atherosclerosis. Hejtmancik and associates[11] observed clinical evidence of heart disease in 13 of 21 patients with acromegaly. In 5 there was frank cardiac failure. Pathologic studies in 4 cases disclosed marked cardiac hypertrophy in all and diffuse interstitial fibrosis in 2. Cardiac abnormalities are not associated with gigantism unless acromegaly is also present.

The pathogenesis of the association of atherosclerosis and cardiac hypertrophy to acromegaly is uncertain. The common occurrence of diabetes in acromegaly[3] (adrenotrophic or pituitary diabetogenic hormone) is worthy of attention in view of the striking association of diabetes with premature and advanced coronary atherosclerosis (p. 1034). Hyperthyroidism, which accompanies acromegaly frequently, has been given as a cause for the cardiac hypertrophy, but this relationship is questionable.

It is more probable that the excessive cardiac hypertrophy results from the hypertension and from progressive heart failure due to hypertensive and atherosclerotic heart disease. Hypertension was found frequently in the 21 cases analyzed by Bartelheimer[1] and was attributed to concomitant hyperfunction of the basophile portion of the anterior pituitary lobe. The occurrence of heart failure was stressed in the collection of 25 cases of acromegaly recorded by Fournier.[9] Heart failure and hypertension were observed in the patient studied by Humphry and Dixon,[13] whose heart subsequently was found to weigh more than 1100 gm. Similarly the remarkable cardiac enlargement in Zondek's[16] case could be explained by the blood pressure of 210/140 and by the dyspnea and cyanosis indicative of cardiac insufficiency. Courville and Mason[4] reported that pronounced heart failure was present in 18 (75 per cent) of their patients

with acromegaly Weakness, attacks of syncope breathlessness and anasarca were the outstanding manifestations often in contrast with the false appearance of physical strength presented by these individuals The electrocardiogram disclosed left axis deviation, widening and slurring of the QRS and occasionally T wave changes late in the disease Bartelheimer[1] found electrocardiographic evidence of myocardial damage in 14 of 21 cases of acromegaly

BASOPHILISM—CUSHING S SYNDROME

See Hyperfunction of Adrenal Cortex below

PITUITARY INSUFFICIENCY—SIMMONDS DISEASE

With respect to the heart, the effects of pituitary insufficiency may be similar to those described under myxedema (p 1016), or to those described under Addison s disease (p 1028) The heart participates in the generalized atrophy of the various organs Microscopic examination may di close brown atrophy of the heart and degeneration of the muscle fibers The electrocardiogram shows very low voltage of the QRS complexes and low, flat or diphasic T waves in standard leads [8] Congestive heart failure has been reported in association with pituitary myxedema [9]

THE ADRENAL GLANDS

HYPERFUNCTION OF THE ADRENAL CORTEX—CUSHING S SYNDROME

Hyperfunction of the adrenal cortex usually due to benign or malignant neoplasms, may cause the adrenogenital syndrome or Cushing s syndrome The former is characterized by sexual precocity, hermaphroditism virilism of females or feminization in males, loss of libido etc These cases in pure form, are not associated with distinctive cardiovascular manifestations However, in an 8 year old female with the adrenogenital syndrome complicated by hypertension there was found a defect in steroid biogenesis, namely, an inability to hydroxylate the steroid nucleus at carbon–11 The entire clinical picture including the hypertension was reversed by small doses of compound F [21a]

Cushing s syndrome [8] occurs chiefly in women and is characterized by obesity especially of the trunk, neck and face (moon face) hirsutism amenorrhea and loss of libido, bluish abdominal striae, hypertension hyperglycemia and tendency to glycosuria hypercholesterolemia, osteoporosis, especially of the spine (kyphosis), and polycythemia Many of these features are obviously similar to the effects of stimulation of the anterior pituitary gland

The most important findings with respect to the heart are hypertension, which may be of intense degree and associated cardiac hypertrophy Renal insufficiency and death from a cerebral accident may result from malignant hypertension [11, 67] In a case which I observed and which was studied and reported by Oppenheimer and Silver,[65] there was malignant hypertension, severe hypertensive neuroretinitis renal insufficiency (azotemia) and hyperglycemia Eventually death resulted from congestive heart failure

Glycosuria diminished glucose tolerance or frank diabetes is observed in many cases of Cushing s syndrome [79] This association of diabetes and hypertension, noted previously in connection with acromegaly, is of interest because it is commonly found in combination with severe coronary atherosclerosis in cases not due to apparent endocrinopathy These relationships suggest the possibility that hypertension diabetes and coronary atherosclerosis are not haphazard associates but the result of some common endocrine metabolic factor

The hypertension observed in patients with Cushing's syndrome due to adrenal cortical tumors is probably due to an hypertensive factor secreted by the adrenal cortex This belief is supported by the observation that the synthetic steroid desoxycorticosterone produce a progressive and sometimes alarming increase of blood pressure in patients with adrenal insufficiency (Addison's di ea e) [33, 74] as well as a less pronounced elevation of blood pressure in normal man [11] The reversal of the hypertension as well as the other manifestations of Cushing s syndrome following removal of an adrenal cortical tumor, substantiates the causal relationships between the adrenal cortical tumor and the hypertension in these cases The administration of excessive amounts of desoxycorticosterone to patients with Addison s disease is followed not only by hypertension, but also by subcutaneous edema and other signs of congestive heart failure, such as gallop rhythm enlargement of the heart, increased venous pressure

and roentgenologic evidence of pulmonary congestion [35, 83, 27] It is probable that these manifestations are the consequence of excessive sodium and water retention due to the effect of desoxycorticosterone on renal excretion of sodium I have also observed the development of angina pectoris simultaneously with hypertension and peripheral edema in a man with Addison's disease who received an excessive amount of desoxycorticosterone from implanted pellets of this substance

The natural sodium retaining (and potassium excreting) hormone of the adrenal cortex is aldosterone which is excreted in excessive quantities in heart failure (p 173) A clinical syndrome due to primary aldosteronism has been described It is characterized by hypernatremia hypokalemia alkalosis with periodic severe muscular paralysis intermittent tetany and paresthesia polyuria polydypsia and hypertension but no edema [26]

Electrocardiographic changes involving the T wave were noted by Raab[69] after giving desoxycorticosterone to normal men but these changes were not striking Currens and White [7] described much more pronounced abnormalities when excessive amounts of this substance and sodium chloride were administered to patients with Addison's disease There was a progressive diminution in the voltage of the QRS and T waves and subsequent isoelectric or inverted T waves in leads I and II These patients also developed congestive heart failure The T wave changes were similar to those attributed to hypokalemia in familial periodic paralysis [59]

HYPERFUNCTION OF THE ADRENAL MEDULLA—PHEOCHROMOCYTOMA PARAGANGLIOMA

Tumors of the chromaphil tissue of the adrenal medulla (pheochromocytoma) or of the extra adrenal chromaphil cells in the sympathetic paraganglia in the lumbar paravertebral region of the abdomen in the organ of Zuckerkandl[38] at the bifurcation of the aorta in the thoracic paravertebral region and in the carotid bodies (paraganglioma) produce excessive amounts of norepinephrine and epinephrine which are constantly or paroxysmally secreted into the blood stream [19, 5] Pheochromocytomas were encountered in 0 5 per cent of a series of hypertensive patients[61] but the incidence is probably even lower They are bilateral in about 10 per cent of cases and more frequent on the right than on the left side [45] Occasionally they occur in siblings and other members of the same family They may occur in young children [29] Neurofibromatosis and retinal angiomata may be associated [31, 40]

The clinical manifestations of these tumors often alarming in severity are those to be anticipated from the vasopressor effects of injecting large doses of norepinephrine and the cardiac and metabolic effects of epinephrine Patients with pheochromocytoma or paraganglioma usually exhibit paroxysms (minutes or hours) of severe hypertension (200 to 300 mm Hg) anxiety and tremulousness palpitation with tachycardia or bradycardia severe throbbing headache and nausea or vomiting glycosuria and pronounced vasomotor phenomena including pallor or flushing and sweating [11] and occasional dyspnea substernal or precordial pain or gooseflesh Neurologic complications especially cerebral hemorrhage occur in about 15 per cent[18] and rupture of an intracranial aneurysm has been reported [22] An increased basal metabolic rate occurs commonly and may lead to a mistaken diagnosis of hyperthyroidism Attacks of acute pulmonary edema occur in about half the cases Acute pulmonary edema in young individuals without cardiac or valvular disease and without cardiac enlargement should suggest the presence of pheochromocytoma During pregnancy pheochromocytoma may produce symptoms resembling those of preeclampsia Electrocardiographic changes may appear during the paroxysm e g atrial fibrillation deformed ventricular complexes and atrioventricular dissociation [24] Death may result from an acute coronary occlusion or a cerebral accident

Of particular interest are the cases in which the hypertension associated with pheochromocytoma is not paroxysmal in occurrence but persistent and severe [67] The latter have been observed more frequently than the former [41] These cases of persistent hypertension may simulate and be mistaken for cases of essential hypertension of the so-called malignant type Persistent hypertension due to pheochromocytoma or repeated paroxysms over a long period may be associated with vascular changes in the fundus cardiac enlargement and renal insufficiency

It is important to recognize such cases be

cause of the possibility of successful excision of the causative tumor with cure of the clinical symptoms including regression of the fundal, cardiovascular and renal abnormalities[21, 50] Furthermore, patients with unrecognized pheochromocytoma may die from shock due to incidental operations[6]

Diagnosis of Pheochromocytoma

The diagnosis may be made readily if the physician is familiar with the clinical picture and sees the patient during an attack The following manifestations in association with hypertension singly or in combination suggest the possibility of a pheochromocytoma attacks of palpitation attacks of pulmonary edema in young persons without heart disease excessive sweating vasomotor phenomena, hypermetabolism, hyperglycemia or glycosuria postural tachycardia and postural hypotension normal cold pressor response Between attacks the diagnosis may be suggested by the history of the paroxysms if the physician is mindful of the condition In patients with chronic hypertension due to pheochromocytoma the presence of the latter may be suggested by a history of paroxysms during which the chronically elevated blood pressure is sharply increased and by the finding of associated hypermetabolism and glycosuria or hyperglycemia[80] Confirmation in any of the above circumstances depends on pharmacologic or chemical tests for excessive secretion of epinephrine and norepinephrine[66] and on roentgenologic demonstration of a 'tumor' shadow in the adrenal region

In practice the pharmacologic or chemical tests (infra) are performed for screening purposes Then intravenous and, if indicated, retrograde pyelograms are performed and these may suggest the presence and site of an adrenal tumor Laminograms of the adrenal regions may occasionally disclose the tumor or tend to exclude its presence by revealing normal sized adrenal glands Perirenal insufflation has been used extensively but has come to be regarded by many as too hazardous a procedure At present carbon dioxide or oxygen is introduced into the presacral region, resulting in an equally satisfactory method of contrast visualization of the perirenal area without the hazard of perirenal insufflation[6, 8, 88] If a sympathectomy is performed for severe hypertension the adrenal glands should be inspected for the presence of a tumor

Tests for Pheochromocytoma (Paraganglioma)

1 **Pressor Drugs.** These are employed between attacks to provoke a rise in blood pressure in patients with paroxysmal hypertension or in those with slight chronic hypertension and paroxysmal crises They should not be used in patients whose systolic blood pressure is more than 170 mm Hg or whose diastolic pressure exceeds 110 mm Hg *Histamine* is the test drug of choice[73] Mecholyl[47] has been found to be much less reliable and TEAC (tetraethylammonium chloride or Etamon)[53] has resulted in too many false negative tests[3]

Technique The patient lies quietly for 15 minutes or more until the blood pressure is stabilized, as determined by repeated measurements at one minute intervals Sedatives should not be given An intravenous infusion of 5 per cent glucose in water is started and the blood pressure is determined repeatedly until the effect of the procedure has worn off and the blood pressure has returned to its pre infusion level

Histamine, in a dosage of 0 025 mg is infused *rapidly* through a three way stopcock attached to the intravenous infusion The blood pressure is then measured and recorded every thirty seconds for five minutes, and every minute thereafter for an additional ten minutes

A *positive response* is denoted by a rise of 60 mm Hg or more in the systolic blood pressure and 30 mm Hg or more in the diastolic blood pressure, occurring within the first five minutes after injection of the histamine and subsiding usually within the next ten minutes Among 21 definite positive tests there was an average systolic rise of 111 mm Hg (range 60 to 200) and an average diastolic rise of 60 mm Hg (range 30 to 110)[8] Benzodioxane should be readily available and 15 to 20 mg should be injected intravenously if there is a severe pressor reaction Serious reactions and even death have been reported[22] Several false negative and two possible false positive tests have been noted[3] The value of a positive histamine test may be enhanced if a cold pressor test[48] is also performed and the histamine pressor response exceeds that due to immersion of the hand in ice water for five minutes[8] The positive histamine test may be a more accurate indicator of pheochromocytoma if it is followed by a negative reaction after the previous administration of Dibenamine

2 Depressor Drugs These are designed to cause a rapid reduction in blood pressure in patients with sustained hypertension They are employed whenever the presence of pheochromocytoma is suspected in patients with persistent hypertension (systolic blood pressure above 170 and diastolic above 110 mm Hg) and in all hypertensive patients under 40 unless the hypertension is clearly due to renal disease Regitine, Benzodioxane and Dibenamine[85] have been employed but Dibenamine has given too high an incidence of false positive tests to be useful

Regitine (phentolamine C 7337) a drug of the imidazoline series is adrenolytic (i e it blocks the effects of norepinephrine and epinephrine) in small doses and a sympatholytic in higher concentrations The Regitine test is simple to perform and free of unpleasant side effects [illegible, 53, illegible, 64] It is therefore most useful to use Regitine as an office procedure for purposes of screening False negative tests are very infrequent However since Regitine may yield a false positive test [71] a positive Regitine test should be followed by a Benodaine test which rarely gives a false positive result No sedatives narcotics anesthetics or antihypertensive drugs should be given for at least 24 hours and no thiocyanates for at least a week prior to the test These drugs or the presence of uremia may account for some or many of the false positive tests with Regitine as well as with Benodaine [33, 39]

Regitine may be administered intravenously or intramuscularly but the latter method is less satisfactory The patient rests in the supine position and the blood pressure is determined at one minute intervals until it is stabilized (at hypertensive levels of 170/110 or higher) Five mg of Regitine methane sulfonate (phentolamine methanesulfonate) in 1 cc of sterile distilled water is injected rapidly intravenously in adults (or 1 mg in children) The blood pre sure is determined and recorded every 30 seconds for 3 minutes then every minute until it returns to its pre injection level (usually within an additional 7 minutes) A positive test is indicated by a maximal fall of more than 35 mm Hg in the systolic pressure and more than 25 mm Hg in the diastolic pressure within two minutes with a rapid return to previous levels usually in 10 to 15 minutes When the drug is injected intramuscularly blood pressure determinations are recorded every 5 minutes for a half hour A positive test is indicated by a fall of more than 35 mm Hg in the systolic and more than 25 mm Hg in the diastolic pressure within 20 minutes after injection The maximal hypotensive effect usually persists for approximately 30 minutes and the blood pressure gradually returns to normal in 3 or 4 hours

Tachycardia is the only side effect observed following the intramuscular injection of Regitine but occasionally weakness dizziness and flushing occur following its intravenous injection

Ben odioxane Test [43, 8] Benzodioxane (piperoxane hydrochloride or 933F or Benodaine) blocks the pressor responses of both epinephrine and norepinephrine

The patient rests quietly and blood pressures are determined and recorded every few minutes until stable A slow intravenous drip of 5 per cent glucose in water is started and after the blood pressure has again stabilized Benodaine is administered at a uniform rate through a three way stopcock attached to the infusion over a 2 minute period The dose is 0 25 mg per kilogram of body weight or 10 mg per sq meter body surface area up to a maximum dose of 20 mg The usual adult dose is between 15 and 20 mg Blood pressure determinations are made and recorded by an assistant during the injection and every 30 seconds thereafter for five minutes and thereafter every minute for 15 minutes

Many hypertensive patients *without pheochromocytoma* exhibit a slight rise in blood pressure after Benodaine or an initial brief hypotensive effect followed by a pressor effect A *positive ben odioxane test* is characterized by a prompt fall in blood pressure of at least 30 mm Hg in the systolic and 30 mm Hg or more in the diastolic blood pressure within 1 to 4 minutes after beginning the injection of benzodioxane The fall in pressure persists at least 5 minutes and is not followed by an elevation of the blood pressure above the pre injection level False positives are very rare except in patients with uremia [illegible, 33, 81] But false negative tests occur occasionally [25, illegible, 3]

Benzodioxane produces mild side reactions frequently and alarming ones occasionally The mild reactions include flushing palpitation apprehension throbbing in the head substernal pressure and hyperpnea [95] The more serious reactions are characterized by striking pressor effects in hypertensive pa

tients.[20] Amyl nitrite pearls or Hydergine may be administered for severe hypertensive reactions and Levophed (norepinephrine) or Neosynephrine (phenylephrine) may be administered in the intravenous drip for the rare severe hypotensive reaction.

Direct Estimation of Catechol Amines[42, 94] (Epinephrine and Norepinephrine) in plasma and urine. Lund[56] reported detectable amounts of norepinephrine in the blood of patients proven to have pheochromocytoma but not in normal individuals or patients with essential hypertension. Similar observations were made by Manger et al who suggested that chemical estimation of the pressor amines in plasma could be valuable as a screening test in patients suspected of having pheochromocytoma. Von Euler[92] observed a marked increase in the urinary excretion of norepinephrine and epinephrine in patients with pheochromocytoma, with a reduction or return to normal urinary excretion following removal of the tumors. Goldenberg and associates[42] have been determining chemically the urinary content of catechol amines as a basis of the diagnosis of pheochromocytoma and have found this to be more reliable than the pharmacologic tests. If further experience confirms its reliability and if the technique is simplified, this urinary test for catechol amines may well replace the pharmacologic tests. Recently Moulton and Willoughby[63] determined the urinary excretion of epinephrine and norepinephrine by bioassay after injection of the urine into cats.

Treatment of Pheochromocytoma

Cure of pheochromocytoma can be expected after its surgical removal.[97] Occasionally the tumor is malignant. From the surgical viewpoint the important aspects are accurate localization, operative technique and management of the patient during and after extirpation of the tumor.[3, 24] The patient must be managed with great care and watchfulness during positioning on the table during induction of anesthesia[17] and during handling of the tumor in order to avoid dangerous paroxysms caused by excessive release of norephinephrine and epinephrine. Regitine hydrochloride tablets (50 mg. each) may be administered orally to control hypertension while the patient is awaiting surgery and Regitine methanesulfonate may be injected intermittently during the operation to control rises in blood pressure. Other adrenolytic or hypotensive agents such as piperoxan (Benzodioxane), Dibenamine or amyl nitrite have also been used to control hypertensive crises during the operation. After the tumor has been removed profound hypotension may occur and blood or dextran infusions as well as pressor drugs (Levophed) may have to be administered.

HYPOFUNCTION OF THE ADRENAL CORTEX—ADRENAL INSUFFICIENCY—ADDISON'S DISEASE

Addison's disease, in which severe adrenal insufficiency results from tuberculosis or diffuse atrophy of the adrenal cortex, is characterized by profound asthenia, striking hypotension, brown pigmentation and by acute crises which are dominated by nausea and vomiting, dehydration, fever and shock due to loss of sodium and water.

The profound weakness overshadows any cardiac symptoms in the chronic untreated state, but dyspnea and palpitation are common. These symptoms are mitigated by the limited activity which the patient's asthenia permits. Hypotension is characteristic during the chronic and acute phases and is the most constant cardiovascular manifestation. The blood pressure is usually below 100 mm. Hg and often between 80 and 90. The diastolic pressure is usually between 60 and 70 mm. Hg and the pulse pressure is low. During a crisis the systolic pressure falls below 80 and often to such low levels that it is unobtainable. The fall in blood pressure is due to deficiency of adrenal cortical hormone and not to lack of medullary epinephrine, for the blood pressure can be restored to normal or even hypertensive levels by the administration of sodium chloride and desoxycorticosterone (p. 1024). The occurrence of frank evidences of congestive heart failure in patients with Addison's disease following excessive desoxycorticosterone therapy, has also been discussed (p. 1024).

The heart in Addison's disease, as in anterior pituitary insufficiency, is small in size and shows poor filling (i.e., it is hypodynamic) on fluoroscopic examination. To some extent the smallness of the heart parallels the severity of the disease and conversely the cardiac silhouette enlarges following treatment with sodium and desoxycorticosterone.[60, 61] In fact the varying size of the heart has been utilized as a guide to treatment with desoxycorticosterone, for according to McGavack[61] an abnormally large cardiac silhouette on teleo-

roentgenograms was the first and most reliable sign of excessive dosage The small size of the heart in Addison's disease is probably due chiefly to the reduction in blood volume, i e, to the proportionally small volume of blood in the cardiac chambers and the consequently low diastolic tension However the loss of potassium and water from heart muscle as well as other muscular tissue[93] has also been cited as a factor in diminishing the size of the heart

The electrocardiogram of Addison's disease often discloses low voltage of the QRS complexes and may show small isoelectric or rarely diphasic or inverted T waves which suggest the presence of myocardial disease [77, 96] In a study of 90 patients with Addison's disease Somerville et al [94] found the electrocardiogram to be normal in 48 per cent, and abnormal in 52 per cent of the cases The electrocardiographic changes observed were as follows in order of frequency (1) flat or inverted T waves especially in left precordial leads (2) prolonged Q T interval, (3) low voltage of the QRS complexes, (4) prolonged P R and QRS intervals, (5) depressed RS-T segment (6) prominent U waves, especially in cases treated with desoxycorticosterone Many of the changes may be related to alterations in potassium metabolism (infra) associated with Addison's disease [53] According to Somerville et al the electrocardiographic changes in Addison's disease are reversed by cortisone but not by desoxycorticosterone

At postmortem examination the heart is usually described as atrophic [75] There may be remarkable degenerative alterations of the muscle fibers but as a rule there are no striking microscopic changes Somerville et al [94] described localized areas of myocardial necrosis and fibrous tissue replacement in 3 of 5 fatal cases which they studied Goodof and MacBryde[44] reported interesting findings in the heart of a patient with Addison's disease who had been treated with desoxycorticosterone and subsequently died of cardiac failure Throughout all four chambers there were foci of necrosis resembling closely similar lesions in the hearts of rats which had received large amounts of desoxycorticosterone[30] and also resembling those lesions produced in rats which had been maintained on a low potassium diet [73, 35] The implication is that desoxycorticosterone administered to patients with Addison's disease causes retention of sodium and fluid with simultaneous excretion of potassium, this sudden reduction in serum potassium especially if the patient is on a low potassium intake is capable of producing cardiac damage and contributing to the development of congestive heart failure Thus myocardial disturbances and corresponding electrocardiographic changes (infra) have been attributed both to the high serum potassium which accompanies Addison's disease and to the reduction in serum potassium which follows effective treatment with desoxycorticosterone and sodium salts

THE HEART IN POTASSIUM DISTURBANCES

Potassium is the predominant intracellular electrolyte (90 to 150 mEq /L) The extracellular and serum concentration of potassium normally ranges from 3 5 to 5 mEq /L A normal concentration of intracellular and extracellular potassium is essential for normal myocardial contraction In the isolated heart potassium antagonizes the tendency of calcium to cause systolic standstill (calcium rigor) When present in excess potassium prolongs diastole and may cause complete inhibition with arrest of the heart Various observations have suggested an intimate relationship between the potassium ion and the action of acetylcholine the humoral effector agent produced by vagal stimulation Potassium may participate in nerve stimulation and muscular contraction by altering cell permeability Changes in the concentration of potassium may produce clinical symptoms due to impairment of muscular activity, and/or changes in the cardiac mechanism and in the electrocardiogram

Anatomic changes in the heart have been described not only in rats maintained on potassium deficient diets [73, 88, 10] but also in patients with hypokalemia of varied etiology Widespread myocardial fibrosis and areas of focal necrosis have been observed [113, 115, 104] However the electrocardiographic changes are more probably due to electrophysiologic disturbances rather than to the anatomic myocardial lesions [102] In cases with low serum potassium the potassium gradient across the cell is increased the speed of exit of potassium is accelerated and the transmembrane action potentials are altered These changes in gradient and action potentials account for the observed alterations in the ST segment T wave and U wave Conversely elevation of

serum potassium diminishes the transcellular potassium gradient and accounts for the tall peaked T waves and other changes

HYPERKALEMIA

In the presence of normal renal function, only slight increases in serum potassium can be induced by potassium infusions or by increased oral intake of potassium But significant hyperpotassemia may occur in various forms of renal insufficiency with uremia, especially in cases of acute tubular nephrosis with severe oliguria or anuria Hyperkalemia is also encountered clinically in cases of Addison's disease and in the untreated stage of diabetic acidosis and in sickle cell anemia The clinical picture is characterized by paresthesias mus

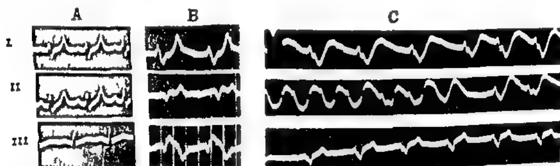


Fig 154 Hyperpotassemia in acute anuria following 7 month stillborn delivery At autopsy two days later bilateral hemorrhagic necrosis of renal cortex
A 3-12-50 K = 7 9 Na = 117 mEq /liter Tall peaked T waves
B 3-13-50 K = 8 5 Na = 120 Tall T wide QRS absence of P wave
C Ventricular tachycardia ventricular flutter fibrillation

cular weakness and flaccid paralysis of the extremities shock, bradycardia and cardiac arrest

The electrocardiogram of hyperkalemia [89, 5, 109, 105, 11] (Fig 154) is characterized by (1) Tall peaked T waves which occur early In children, the negative T waves in leads III and V_1 may become more negative The negative T waves in cases of left ventricular hypertrophy may become upright (2) Lowering of the R and increased depth of S wave (3) Widening and then disappearance of the P wave (4) Progressive widening of the QRS Occasionally this is associated with an apparent elevation of the RS T junction and a cove plane RS T segment and T wave in aV_L resembling the changes seen in myocardial infarction or pericarditis [111, 106] The electrolyte basis for these changes denoting a "current of injury" is indicated by the prompt abolition of the RS T segment elevations when electrolyte imbalance notably hyperkalemia is corrected by hemodialysis [106] (5) Prolongation of the P R interval (6) ST depression The widened QRS becomes smoother obliterates the T and assumes a diphasic appearance resembling a continuous sine wave Eventually ventricular flutter, fibrillation and standstill may occur with high but variable levels of serum potassium (Fig 155) Although there may be no electrocardiographic changes with slight elevations in serum potassium concentration and an imperfect correlation with moderate or large elevations electrocardiographic changes usually appear when serum potassium exceeds 6 5 to 7 4 mEq /L and severe changes are present with concentrations above 7 5 mEq /L [11] A depressed serum sodium or a depressed serum calcium concentration enhances the electrocardiographic effects of a given elevated serum potassium level Acidosis simulates and likewise enhances the electrocardiographic effects of hyperkalemia

If there is chemical, clinical or electrocardiographic evidence of hyperkalemia potassium intake should be interdicted otassium free resins may be administered orally and hypertonic glucose in saline or in distilled water with insulin intravenously If serious hyperkalemia persists it should be corrected with the aid of peritoneal dialysis or the artificial kidney

HYPOKALEMIA

Hypokalemia is most strikingly associated with the syndrome of familial periodic paralysis,[101] but is also encountered in cases of prolonged diarrhea prolonged vomiting fi

tulae with continued external drainage of intestinal fluids, nasogastric suction, intestinal intubation, postoperative infusions of potassium free intravenous fluids when there is no oral intake of food, in some cases of Cushing's disease, in primary aldosteronism, in some cases of chronic nephritis, following vigorous use of cathartics, following ACTH or cortisone, following treatment of diabetic ketosis with insulin, and occasionally in Addison's disease treated with DOCA.

Hypokalemia is characterized clinically by drowsiness, anorexia, nausea, marked muscular weakness progressing to paralysis, and diminution or loss of deep reflexes. The paralysis begins in the extremities and eventually involves the muscles of swallowing and of respiration. Involvement of the respiratory muscles results in the fish mouth type of respiration. Chronic ileus may occur due to disturbed gastrointestinal function.

Electrocardiographic changes are frequently absent in the presence of hypokalemia[116] but usually they are observed when the serum potassium concentration is below 3 mEq./L.[110] On the other hand, electrocardiographic changes due to the depletion of total body potassium may be observed when the serum potassium concentration is within the normal range. The electrocardiographic changes associated with potassium depletion are characterized by (1) depression of the ST segment and lowering, flattening or inversion of the T wave, (2) prolongation of the Q-T interval, (3) presence of an elevated, broad or diphasic U wave which may be responsible for the impression of a prolonged Q-T interval[104] (the combined T and U waves may form a double humped or triple contour), (4) occasional prolongation of the P-R interval. In addition many arrhythmias associated with digitalis administration occur more readily in the

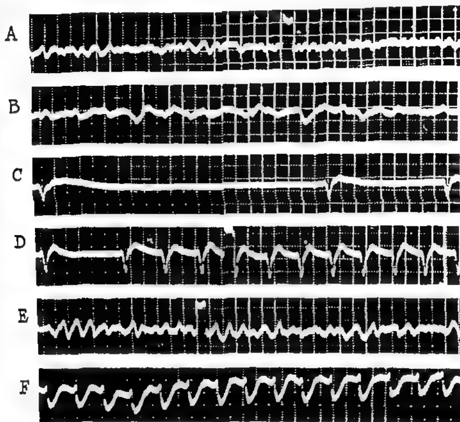


Fig. 155. Hyperpotassemia in acute anuria treated by exsanguination transfusion. Segments of a continuous strip over a five minute period.
A and *B*. Ventricular fibrillation. *C*. Ventricular standstill. *D*. Ventricular tachycardia, rate 130. *E*. Ventricular flutter-fibrillation. *F*. Ventricular tachycardia with intraventricular block.

presence of potassium depletion The electrocardiographic changes are reversed by the oral or intravenous administration of potassium Bellet et al[109] described a variety of electrocardiographic patterns associated with hypokalemia, depending on the causative mechanism Diabetic acidosis was associated with inversion of the T wave and with a prominent U wave whereas in cases of hypokalemia associated with vomiting there was *depression of the RST segment, with a flat* upright T wave or a normal T wave and an elevated U wave

ACIDOSIS AND ALKALOSIS[99]

Metabolic acidosis produces electrocardiographic effects resembling those of hyperkalemia notably tall, peaked T waves[114] Alkalosis induces electrocardiographic changes like those of hypokalemia, viz, lowering of T waves and prolongation of the Q T interval[107] *Lowering or inversion of T waves during* hyperventilation may be due to alkalosis or to undetermined mechanisms involving neural or electrolyte changes

THE PARATHYROIDS

PATHOLOGIC PHYSIOLOGY

The parathyroid glands are concerned with the regulation of calcium and phosphorus metabolism Their physiologic relationship to *the heart arises from the fact that calcium* (with sodium and potassium) is essential to proper cardiac contraction The perfused isolated heart will stop in diastole if there is no calcium, an excess of calcium causes systolic arrest (calcium rigor) Like digitalis, calcium *increases systolic contraction* Fear of a dangerous potentiating effect is the basis for the purported contraindication to the injection of calcium in digitalized patients (p 268) In dogs perfused with calcium in such a manner as to cause a progressive increase in serum calcium Hoff Smith and Winkler[119] observed bradycardia T wave changes and finally death from ventricular fibrillation or from cardiac standstill They concluded that calcium in low concentration was *a cardiac stimulant, in* high concentration it was a cardiac depressant Injected parathormone produces effects which are somewhat similar to those of calcium namely an early increase in heart rate followed by slowing and by cardiac arrhythmia which is characterized by premature beats and shifting of the pacemaker[118]

HYPERPARATHYROIDISM

Hyperparathyroidism in humans is not associated with distinctive cardiovascular disturbances comparable to those described above as following excessive dosage of calcium or parathormone However a shortening of the Q T interval in the electrocardiogram has been noted,[110] but the degree of shortening was slight and insufficient to be of diagnostic value A shortening of the Q T interval also follows digitalis therapy Hyperparathyroidism is frequently complicated by nephrolithiasis and secondary renal insufficiency In such cases, hypertension and its cardiovascular complications may develop (p 020) Hyperparathyroidism has been mentioned as having a possible role in aging and atherosclerosis because of the increased content of calcium in the tissues in these conditions

HYPOPARATHYROIDISM AND HYPOCALCEMIA

Hypoparathyroidism is usually due to injury or accidental removal of the parathyroids during thyroidectomy It is characterized chemically by a reduction in the serum calcium and clinically by the occurrence of tetany *With respect to the heart,* these various conditions associated with hypoparathyroid or other hypocalcemia are of interest because they are documented electrocardio*graphically by a significant and sometimes* striking prolongation of the *Q T interval*[117,113] The increased duration of the Q T interval is due primarily to prolongation of the ST segment and T wave without significant alteration in duration of the *QRS complex*[12] *As the hypocalcemia is corrected* the Q T interval is restored to normal *Although* a prolongation of the Q T interval is most distinctively associated with *conditions in which* there is hypocalcemia the Q T interval is prolonged in hypokalemia and may … be prolonged on occasion in cases of hypokalcemia diabetic acidosis, alkalosis, beriberi quinidine toxicity heart failure and various forms of myocardial disease in which *there is pronounced* cardiac enlargement and in some cases of advanced heart block *or bundle* branch block The increased Q T interval is somewhat similar to that in cases *of hypokalemia* But in hypocalcemia there is no depression of the ST wave *lowering of the* T wave or presence of a U wave as in hypokalemia

TESTES AND OVARIES

The sex hormones of the testes and ovaries are concerned chiefly with the growth development and functional activity of the sexual organs and with the development of secondary sex characteristics In addition the sex hormones produce certain metabolic effects which resemble those of the adrenal cortex whose hormones are chemically related Thus testosterone the most active of the male hormones (androgens), causes a retention of sodium and fluid probably by its effect on the renal tubules The occurrence of premenstrual edema was mentioned above as an anterior pituitary effect but it may be related directly or indirectly to ovarian function

Tumors of the male or female sex organs are not associated with distinctive physiologic or clinical cardiovascular effects Masculinizing tumors of the ovaries may be responsible for manifestations of the adrenogenital syndrome but the hypertension and metabolic changes seen in Cushing's syndrome are absent Diminution in secretion of the ovaries or testes due to disease or atrophy especially at the menopause may be associated with vasomotor and functional cardiovascular disturbances such as flushes, sweats palpitation and tachycardia Psychic factors are also important in the causation of these symptoms Hypertension often develops at the time of the menopause its relation to the sex glands is uncertain Scherf[121] described electrocardiographic changes including ST segment depressions in all limb leads and lowering of the T waves in women with hypoovarian function These alterations were corrected by estrogen therapy That these minor electrocardiographic deviations are specifically due to ovarian deficiency is questionable Former belief in the existence of heart disease secondary to uterine fibromata has almost completely faded

THYMUS

The thymus has been related in function to the sex glands the pituitary thyroid and adrenals Thymic tumors have been associated with the complete Cushing's syndrome including the hypertension[125] Such tumors have also been associated with but not necessarily responsible for myasthenia gravis Mendelow and Genkins[126] found myocardial changes at autopsy in 6 of 12 cases of myasthenia gravis The abnormalities ranged from scattered focal atrophy and vacuolization of the myofibrils with lymphocytic infiltration to severe myocardial necrosis and reactive myocarditis The severe changes were usually observed in cases with thymoma A persistent enlarged thymus and hyperplasia of the lymphoid tissues (status thymicolymphaticus) are sometimes associated with notable hypoplasia of the heart aorta and other vessels and occasionally with sudden death after minor trauma or infection The relationship of the enlarged thymus and lymphoid tissue to sudden death is obscure In fact the whole concept of status thymicolymphaticus has been rejected[128] Raab[1 7] has attributed sudden death in young individuals to ventricular fibrillation caused by excessive amounts of epinephrine like substances in the heart There was a recent report of sudden death in identical twins who were able athletes[1 4] The autopsy in one disclosed hyperplasia of the thymus and hypoplasia of the aorta but there was also pronounced atherosclerosis Attention has already been directed to recent evidence that acute coronary thrombosis is a common cause of death in young individuals (p 493)

THE PANCREAS

HYPERINSULINISM AND HYPOGLYCEMIA

Excessive secretion of insulin such as occurs in islet cell tumors of the pancreas or over dosage with insulin in the treatment of diabetes mellitus or in the shock treatment of schizophrenia results in hypoglycemia Hypoglycemia may occur also in cases of adrenal, pituitary or hepatic insufficiency and in some diseases of the diencephalon Hypoglycemia is of serious concern to patients with angina pectoris or myocardial damage secondary to coronary atherosclerosis for attacks of angina pectoris and of myocardial infarction have been attributed to too vigorous insulin therapy and consequent hypoglycemia[15 131]

Aside from the serious neuropsychiatric manifestations of hypoglycemia such as anxiety confusion ataxia syncope convulsions and coma there are striking vasomotor and cardiovascular signs such as sweating pallor palpitation tachycardia and a slight rise in blood pressure Many of these effects resemble those due to norepinephrine or epinephrine It may be that they are actually due

to a compensatory secretion of the latter, which tends to restore the lowered blood sugar to normal by converting hepatic glycogen into glucose [138] On the other hand, a reduction in blood sugar may directly interfere with cardiac metabolism and produce effects similar to those caused by myocardial anoxia [134]

In the electrocardiogram, insulin hypoglycemia is documented by a depression of the ST segment, most commonly in leads I II or both, and by low or diphasic T waves in these leads [145] These non specific changes resemble those caused by epinephrine but similar changes are observed in patients with angina pectoris during attacks or after an anoxemia or exercise test (p 408) Similar changes have been described in schizophrenic patients treated with insulin shock In addition to ST depressions and T wave changes, prolongation of the P R and Q T intervals were noted,[140, 139] changes resembling those of hypokalemia and probably due to hypokalemia

DIABETES MELLITUS

The fundamental importance of diabetes in cardiology rests on the frequency with which this disease is accompanied by atherosclerosis and its complications especially coronary artery occlusion [159, 161, 1, 9, 135] It is a striking fact that the mortality from coronary and peripheral atherosclerosis among diabetics has increased sharply despite the fact that carbohydrate metabolism has been controlled and the mortality from acidosis greatly reduced

Advanced coronary atherosclerosis has been encountered in a higher percentage of cases of diabetes studied at autopsy than in those without diabetes [131, 137, 156, 133] Clinical evidence, i e, of angina pectoris and acute myocardial infarction has been observed with much greater frequency among diabetic than among non-diabetic individuals [153, 135, 152, 1, 1] (See also p 493) Whereas coronary occlusion among non-diabetics is very predominantly a disease of males (p 493), among diabetics women suffer an occlusion as often as men [161, 132] This strongly suggests the predisposing effect of diabetes Not only does diabetes appear to enhance the likelihood of developing coronary atherosclerosis, but also it seems to hasten the time of its appearance, for coronary occlusion and other forms of atherosclerosis are encountered among relatively young diabetics [1, 1, 150, 155] The mortality rate from acute myocardial infarction is especially high among diabetic patients 60 8 per cent for all attacks and 57 8 per cent for first attacks in a recently reported series of cases [152] The chances of late survival after myocardial infarction are poor among diabetics, fewer than 20 per cent survived five years and only 3 6 per cent more than ten years [12]

The frequency of atherosclerosis increases with the duration of the diabetes Recent studies indicate that almost every diabetic is an actual or potential victim of advanced atherosclerosis of the heart extremities or retinal vessels [14, 136]

Hypertension is common among diabetics,[1, 1] but an etiologic relationship is uncertain In recent years attention has been directed to the syndrome of diabetes, hypertension and severe albuminuria often with peripheral edema and retinopathy [144, 157] The pathologic basis of this syndrome is an intercapillary glomerulosclerosis Hypertension also accompanies diabetes in cases of angina pectoris or coronary occlusion, especially among women An interesting association of hypertension with diabetes (or diminished glucose tolerance) was mentioned as occurring in cases of acromegaly (p 1023) and Cushing's syndrome (p 1024) Russi et al [146] recently observed that diabetes and hypertension occurred five times as frequently in cases in which examination at autopsy revealed small adenomata of the adrenal cortex as in the cases in which an adrenal adenoma was absent The association of diabetes hypertension and advanced atherosclerosis in patients with gross disease of the anterior pituitary (acromegaly), adrenal cortex (Cushing's syndrome) and thyroid (myxedema) suggests the fruitfulness of a search in the endocrine organs for a possible common denominator in the etiology of these diseases

Hypertension and coronary atherosclerosis in diabetics may be terminated by an acute coronary occlusion Often myocardial disease and strain secondary to coronary atherosclerosis and hypertension lead eventually to clinical manifestations of congestive heart failure A relative deficiency of vitamin B_1 in diabetes mellitus should be considered as a possible contributory factor in the development of heart failure

The common occurrence of acute myo-

cardial infarction in diabetics presents problems in diagnosis and therapy The acute coronary incident is sometimes associated with hyperglycemia glycosuria and ketonuria as well as with shock and occasional nausea and vomiting An erroneous diagnosis of impending coma based on the laboratory findings, may be considered while the cardiac infarction is overlooked On the other hand diabetic coma may actually occur with or be precipitated by an acute coronary occlusion The diabetes is properly diagnosed and treated but the occlusion may not be recognized

The association of acute coronary occlusion with diabetic coma requires special caution in treatment lest an overenthusiastic administration of insulin enhance the myocardial disturbance already present or a too vigorous administration of fluids especially as saline overload the damaged heart and induce congestive heart failure Haste in the correction of shock dehydration and ketosis is essential but continuous clinical observation and chemical study are necessary to avoid a cure of the diabetic acidosis with loss of the patient from cardiac disability Similarly in the treatment of all cases of longstanding diabetes especially in elderly patients it should be assumed that pronounced coronary atherosclerosis is probably present and sharp reductions in the blood sugar by diminishing carbohydrate intake or increasing the dose of insulin should be avoided[160] An intake of less than 125 to 150 gm of carbohydrate daily is rarely advisable Although correction of acidosis is essential and of glycosuria is desirable a moderate hyperglycemia should be maintained as a reserve against excessive reductions in blood sugar This denotes minimal insulin dosage

DIABETIC ACIDOSIS

Certain electrocardiographic abnormalities have been observed in patients during and on emergence from diabetic acidosis and coma[130 147 141] The chief alterations are a prolongation of the Q T interval depression of the ST segment, low and inverted P waves diphasic or inverted T waves, and a prominent U wave which may be fused with the T wave Recent studies have somewhat clarified the relationship between the electrocardiographic changes observed in diabetic acidosis and the stage of treatment of this metabolic disturbance and especially the relation to the concentration of plasma potassium[149] Usually the serum potassium level is elevated at the time of hospital admission of the patient with untreated diabetic acidosis The electrocardiogram may then disclose the tall peaked T waves and other changes distinctive of hyperkalemia Following institution of treatment with insulin and sodium chloride and/or glucose infusions, hypokalemia is induced[143] because of (1) deposition of glycogen with potassium in the liver (2) increased uptake of potassium by other cells, (3) renal loss of potassium due to the intravenous infusions (4) dilution caused by increased plasma and extracellular volume The electrocardiographic changes described above in patients treated for diabetic acidosis are those due to hypokalemia However Henderson[141] found no correlation between the serum potassium level and the degree of cardiac abnormality in 21 of 42 patients with diabetic acidosis and abnormal electrocardiograms and therefore considered intracellular potassium disturbances as the probable cause of the electrocardiographic abnormalities

HEMOCHROMATOSIS

Hemochromatosis or bronze diabetes is a metabolic disease characterized by pigmentation of the skin and internal organs diabetes and frequently cirrhosis of the liver The iron containing pigment is also deposited in the heart muscle in most cases but fibrosis is rare[164 167] In recent years there has been an increasing number of reports of cardiac hemosiderosis in hemochromatosis[1 2 166] Occasionally there have been reports of heart failure in cases of hemochromatosis not explained by the usual forms of heart disease[168 171 165 165] In the case of Kerr and Althausen[169] and in the case reported by Petit[17] complete heart block was present as well as the evidence of heart failure In one of the two cases reported by Lewis,[171] diagnosis was hampered by the absence of diabetes or pigmentation clinically although extensive hemosiderin deposits were found post mortem in the heart and other organs

Cardiac involvement in hemochromatosis usually in children or young adults is indicated clinically by diffuse enlargement of the heart associated with left and right sided congestive heart failure predominantly the latter Substernal or cardiac pain has been noted in a number of cases[168 172] and has led to a mistaken diagnosis of acute coronary

occlusion Low voltage of the QRS complexes and T wave depressions or inversions are observed but no RS-T deviations as a rule[172, 166] Arrhythmias and conduction disturbances[174, 168, 170] are common including paroxysmal tachycardia, atrial flutter, atrial fibrillation, occasional ventricular tachycardia, partial and complete atrioventricular block and intraventricular conduction defects The nature of the cardiac disturbance and the pathogenesis of the heart failure are obscure but the latter has been attributed to extensive deposition of hemosiderin and myocardial degeneration Occasionally there is considerable destruction of muscle and replacement fibrosis[173] But because in many cases the pathologic changes do not appear to account adequately for the development of heart failure it has been suggested that the latter is due to myocardial intracellular biochemical disturbances caused by the hemosiderin deposits with resulting impairment in enzyme systems required for the glycolytic cycle in myocardial metabolism[171]

Treatment of the heart failure may be effective but only temporarily

NUTRITIONAL DISTURBANCES

OBESITY

While obesity is ultimately the result of an excessive caloric intake relative to the metabolic requirements of the body there is considerable evidence that disturbances in the diencephalon and psychic factors may be important in its pathogenesis The relation of endocrine disturbances to obesity is noted in cases of adrenal cortical or anterior pituitary tumors causing Cushing's *syndrome and in* cases of myxedema

With respect to the cardiovascular system obesity has several important relationships There have been many studies which indicate a correlation between obesity and hypertension especially systolic hypertension[195, 185, 191] But the role of obesity in causing false high blood pressure readings must be considered in evaluating such reports (p 921) Weight reduction sometimes effects a fall in the blood pressure of obese hypertensive individuals (p 935) There is also some evidence that coronary atherosclerosis and occlusion are more common in the obese (p 416) The syndrome of extreme obesity, somnolence polycythemia hypoventilation and cor pulmonale has been noted (p 981)

Obesity influences the roentgen ray appearance of the cardiac silhouette and the electrocardiographic tracing Because of elevation of the diaphragm the heart assumes a transverse position and the left ventricle may appear enlarged in the anteroposterior view The presence of a large apical fat pad may enhance this effect by obscuring the apex Views in deep inspiration minimize these distortions In the electrocardiogram the limb leads frequently disclose an inversion of T_3 and left axis deviation[197]

Fatty infiltration of the surface of the heart is common in obese subjects The epicardial fat is increased and encases most of the heart especially the right ventricle and the interventricular sulcus It may even penetrate the superficial muscle bundles[196] But fatty *infiltration* is only rarely responsible for serious heart disease associated with clinical symptoms (p 629) Fatty *degeneration* of myocardial fibers results most often from anemia and infections and occasionally from phosphorus or other poisoning

Moderate dyspnea on exertion is common in obese persons partly because of the abnormal strain of the ballast on the circulation[183] and partly because obese individuals do not exercise and lack training Dyspnea in the very obese or dyspnea which develops concomitantly with pronounced weight gain should be carefully evaluated to avoid misinterpreting it as a symptom of congestive heart failure Excessive weight may also exaggerate symptoms in patients with heart failure due to independent organic heart disease In such cases weight reduction is an important part *of the therapeutic program*

UNDERNUTRITION AND STARVATION[111]

Undernutrition leads to a reduction in cardiac weight which is proportional to or slightly less than the reduction in total body weight[187] This is accompanied primarily by atrophy of myocardial fibers but with prolonged and severe starvation brown atrophy fatty and other degenerative changes appear

The basal metabolism is depressed and the cardiac output (minute volume) as well as the stroke output is diminished The cardiac work is reduced, because of this, undernutrition has been employed in the treatment of hypertension, acute coronary occlusion and heart failure

There is pronounced sinus bradycardia in

severe undernutrition The circulation time is prolonged the venous pressure depressed and the blood pressure and pulse pressure diminished the systolic falling more than the diastolic The extremities tend to be cold pale and slightly cyanotic

There are few *symptoms* referable to the circulatory system Dizziness may occur with sudden rising Syncope may result from prolonged standing Dyspnea palpitation and precordial pain are absent Edema is often a prominent feature but is not attributed to heart failure as the heart is not enlarged and the venous pressure is low or normal The circulating blood volume and extracellular fluid are increased[180]

The electrocardiogram shows in addition to bradycardia a reduction in the voltage of all deflections a prolonged Q T interval (but not necessarily prolonged in relation to the cardiac cycle) right axis deviation and only occasionally depression of the RST segment alteration of T waves and a prolongation of the P R or QRS intervals[181 184] These changes may be due at least in part to deficient potassium and calcium intake

The exact mechanism for *starvation edema* is uncertain The classic belief that it is due to pronounced hypoproteinemia especially to the reduction in plasma albumin was supported by the findings in German civilian internees[180] and in the civilian population of Saipan during the war[189] However this viewpoint has been challenged[183 139] because of the occasional appearance of famine edema when the plasma proteins were normal because of the absence of edema in some instances of hypoproteinemia, and occasional clinical improvement with profuse diuresis and loss of edema before there is a significant change in the concentration of plasma protein These imperfect correlations between hypoproteinemia and edema probably do not invalidate the belief that the latter is due in part to the reduction in colloid osmotic pressure associated with diminution in plasma protein according to the Starling theory However other factors such as variations in tissue pressure presence of dehydration, and especially the degree of inactivity or activity may account for discrepancies Famine edema sometimes diminishes or disappears with bed rest and increases with physical exertion Exercise may increase the venous return beyond the capacity of the atrophic heart to accept, edema may appear or increase because of a consequent elevation of venous pressure

It is probable that edema does not occur in patients with severe undernutrition and starvation despite hypoproteinemia because of minimal or no intake of sodium Commonly, edema in starved individuals appears only after food intake is resumed and sodium is thereby ingested

Although manifestations of congestive heart failure are usually absent even with prolonged starvation they may appear rapidly if nutritional rehabilitation is effected too enthusiastically,[177] or if fluid balance is restored too rapidly Dyspnea tachycardia and cardiac enlargement may develop and there may be a recurrence of edema associated with an elevated venous pressure

Nutritional Heart Disease in Africa (p 637)

Heart disease with right- and left-sided congestive heart failure due to longstanding dietary deficiency occurs frequently in the Bantu in South Africa[14 175] The syndrome differs from beriberi heart disease as described below, in the absence of the hyperkinetic circulation (increased cardiac output, etc) and in the failure to improve with thiamine chloride But there is a satisfactory response to a well balanced diet Extreme generalized edema dyspnea cardiac and hepatic enlargement (due often to pigmentary cirrhosis), gallop rhythm low cardiac output high venous pressure and prolonged circulation time are the most striking features At necropsy, the hearts were dilated and hypertrophied and there were foci of myocardial fibrosis and frequent mural thrombi and peripheral emboli

Kwashiorkor[179] is an African cardiac disease, occurring chiefly in children and characterized by hypoproteinemia, anasarca hepatic fibrosis degenerative myocardial changes involving chiefly the left ventricle and subendocardial fibrosis It is attributed to a nutritional deficiency

VITAMIN DEFICIENCY

Vitamin B_1 Deficiency—Beriberi Heart

Cardiovascular manifestations are often associated with the so called wet form of beriberi These cardiac disturbances were described in cases of beriberi in the Orient by Shimazono[2] and by Aalsmeer and Wenckebach,[197] in cases in this country by Scott and

Herrmann [3] and by Weiss and Wilkins, [4] in Cuban children by Junco[209] and by Abrilli [198] and in Brazil by Benchimol and Schlesinger [176] Weiss and Wilkins [4] were able to report in 1937 on 120 cases of beriberi with cardiovascular as well as neurologic manifestations in the Boston City Hospital an incidence far greater than the occasional case encountered in most hospitals Whereas beriberi in the Orient and elsewhere is due usually to a diet limited to polished rice in this country it has often been observed in alcoholics or drug addicts A restriction in food intake, neurotic adherence to food fads, poverty with consequent caloric and vitamin deficiency, and occasionally diabetes, pregnancy and severe gastrointestinal disease have been causative or contributory factors Pellagra is often, and scurvy occasionally, combined with beriberi in the same patient

Symptoms The cardiac symptoms often start with palpitation, fatigue and rapid heart beat Breathlessness and peripheral edema develop early Progressive dyspnea orthopnea attacks of cardiac asthma or pulmonary edema appear as evidences of left-sided heart failure Increasing subcutaneous edema serous effusions, engorgement of the cervical veins and enlargement of the liver result from failure of the right side of the heart Aalsmeer and Wenckebach[197] described only symptoms of right-sided heart failure in their cases of Oriental beriberi Shock may result from acute cardiac failure or from acute peripheral vasodilatation Late in the disease syncope with fall in blood pressure and other symptoms of shock dominate the clinical picture Sudden collapse is termed *shoshin* in the Far East

Objective Findings Physical examination discloses besides the neurologic signs enlargement of the heart in severe cases muffled first heart sound systolic murmurs embryocardia and gallop rhythm tachycardia and accentuation of the second pulmonic sound In the Cuban cases, murmurs arrhythmias and cardiac enlargement were not observed [209] The superficial veins are engorged and the venous pressure elevated The pulse may be bounding and pistol shot sounds may be heard over the femoral arteries Corresponding to these vascular signs there is a pronounced increase in the pulse pressure, but the mean arterial pressure is normal The pulse rate is rapid The skin is usually warm However, these peripheral vascular phenomena may be absent and the clinical findings may be indistinguishable from those of heart failure due to other types of heart disease

The Electrocardiogram The electrocardiogram may disclose depressed, diphasic or inverted T waves Low voltage of the QRS complexes and a prolongation of the Q T interval occur not infrequently [203] The changes resemble those of and may be due to potassium deficiency Tachycardia is usual With successful treatment there is observed slowing of the heart rate, increased voltage and disappearance of T wave abnormalities

Roentgenologic examination often reveals cardiac enlargement which regresses on a regimen of bed rest and large doses of thiamine chloride [202, 204] Garland and McKenney[207] noted an enlarged poorly contracting heart with mild pulmonary congestion in cases of beriberi heart disease

Morphologic Changes Postmortem examination reveals occasional cardiac hypertrophy but frequently the hearts are of normal weight [2,4] Aalsmeer and Wenckebach[197] stressed the occurrence of right ventricular dilatation Histologic examination usually discloses a normal myocardium but there may be hydropic degeneration of the myocardial fibers, separation of the myocardial bundles swelling of the collagen and perivascular and interstitial "edema" [2,3] The cardiac manifestations of beriberi may be attributed to actual anatomic abnormalities in some cases[2,3] but the lesions described are non specific and often absent It is more likely that disturbances in carbohydrate metabolism incident to thiamine deficiency, produce derangements in energy production and consequently in cardiac function, which may or may not have a visible anatomic basis Recent observations showed that the hearts of thiamine-deficient dogs were unable to absorb pyruvate from the blood as do normal hearts [17] In fact in these animals the T wave changes observed in the electrocardiogram could be correlated with an outpouring of pyruvate from the heart

Pathologic Physiology Many of the cardiovascular manifestations of beriberi probably originate in the peripheral vascular system and resemble those encountered in anemia hyperthyroidism fever or arteriovenous fistula Peripheral vasodilatation i e diminished peripheral vascular resistance may result from acidic metabolites (pyruvic and lactic acid) These accumulate because of the

lack of thiamine which is essential for cocarboxylase, *the enzyme required to oxidize* pyruvic acid The coefficients of myocardial extraction for lactate, pyruvate and oxygen were found to be significantly decreased in thiamine-deficient dogs[184] Thus thiamine deficiency affects cardiac action as well as the peripheral circulation

The diminished peripheral resistance has the effect of multiple arteriovenous shunts which greatly accelerate the speed of the circulation However Keefer[10] noted accelerated circulation in only one third of the cases he observed in China and Blankenhorn et al[202] stressed that acceleration of the circulation is rare in Occidental beriberi as observed in this country In the presence of heart failure the circulatory acceleration due to uncomplicated beriberi may be obscured or because of mental dulness it may be difficult to perform a reliable test of circulation time When the speed of the circulation is accelerated the venous return and the minute cardiac output are increased[174 190] Nevertheless heart failure occurs despite the abnormally great cardiac output because although elevated the output is still relatively inadequate to supply the tissues whose oxidative metabolism is impaired The venous pressure becomes elevated Oxygen consumption is increased and the arteriovenous difference is small[14] Heart failure in beriberi may be considered to result from (1) the thiamine-deficient metabolism *of heart muscle*[184] *(2) increased work of the* heart due to augmented venous return and cardiac output It is probable that there is a stage of beriberi in which the circulation is accelerated and the venous return and minute volume increased without congestive heart failure just as there are prefailure stages of increased circulation in arteriovenous fistula and hyperthyroidism

Diagnosis The diagnosis of beriberi heart is based on the recognition of the cardiovascular abnormalities in association with other evidences of beriberi such as tenderness and swelling of the calves and peripheral neuritis in subjects with a history of dietary deficiency and/or chronic alcoholism There may also be concomitant signs of pellagra and occasionally of scurvy such as psychosis dermatitis glossitis diarrhea anemia dysphagia and purpura Beriberi heart must be considered as the etiologic type in all cases of unexplained cardiac enlargement or unexplained cardiac failure A normal or diminished circulation time *in the presence of heart failure suggests beri* beri heart if hyperthyroidism can be excluded and fever is absent Severe anemia of various etiologies may produce somewhat similar circulatory disturbances but should not lead to confusion with beriberi heart In the American cases of beriberi heart disease rapid circulation is often absent or insignificant or it may be overshadowed by the slowing due to congestive heart failure The response to the administration of thiamine chloride is of diagnostic importance but failure to improve does not exclude the diagnosis of beriberi heart disease Above all a careful dietary history may aid in supporting or rejecting the diagnosis of beriberi heart On the basis of 10 cases studied at the Cincinnati General Hospital Blankenhorn[01] emphasized the following diagnostic criteria (1) enlarged heart with normal rhythm (2) dependent edema (3) elevated venous pressure (4) peripheral neuritis or pellagra (5) gross deficiency of diet for three months or more (6) no other cause for the heart disease (7) clinical improvement and reduction of heart size after specific treatment In recent years there has been a tendency to liberalize the diagnostic criteria of beriberi heart disease and to consider this diagnosis in all cases of heart failure of obscure origin in which there is a history of dietary deficiency in thiamine chloride[199]

Treatment Thiamine chloride given sub*cutaneously in doses of 100 mg daily is the* specific treatment An adequate protein intake is important for the proper utilization of thiamine In most instances in which the disease is not of long duration or far advanced the response is extremely favorable and rapid Signs of congestive heart failure including anasarca disappear first later the enlarged heart returns to normal size[07] and the electrocardiographic abnormalities disappear On the other hand too zealous a caloric intake may at first induce an exacerbation of symptoms Occasionally in cases of chronic thiamine deficiency the myocardial changes are irreversible or only partially reversible The clinical response may be slow or unsatisfactory Relapses after apparent recovery are not uncommon

Rest in bed is an important adjuvant in therapy Anasarca may disappear after rest in bed alone Conversely, as in cases of edema due to undernutrition, exercise intensifies the

manifestations of the disease or may precipitate a recurrence following recovery Sodium salts should be restricted Mercurial diuretics should be given as in other cases of congestive heart failure but their effectiveness will be only slight or moderate so long as the vitamin deficiency is uncorrected Digitalis is ineffective possibly because it acts on the energy utilization phase of myocardial contraction whereas beriberi heart disease is related to defective energy production Other vitamin deficiencies should also be corrected by the administration of niacin, ascorbic acid vitamin K, etc and a high caloric diet rich in protein should be given Correction of the anemia may require iron liver and/or folic acid Since infection may precipitate cardiac symptoms when there is an underlying vitamin B deficiency[219] this factor should be sought and eliminated

Pellagra

Pellagra is often combined with beriberi It is probable that the cardiovascular disturbances formerly attributed to pellagra are due entirely or chiefly to beriberi However electrocardiographic abnormalities have been correlated specifically with pellagra or niacin deficiency[211] Feil[206] noted electrocardiographic alterations in 40 per cent of 38 cases of pellagra Most commonly there was an inversion of T_1 or T or both (16 per cent), coronary T wave (13 per cent), inversion or eversion of ST, large T in at least one lead and low voltage (18 per cent) Q T was slightly lengthened in some cases There were no roentgenologic abnormalities and no pathologic lesions were discovered at postmortem examination



Fig 156 Glycogen storage disease in an adult Generalized cardiac enlargement

Similarly Porter and Higginbotham[18] observed electrocardiographic abnormalities in 10 of 25 cases of pellagra, but they interpreted the changes as non specific and due to vascular or toxic complications More recently Rachmilewitz and Braun[216] described 16 cases of pellagra in which electrocardiograms disclosed T wave inversions which reverted to normal after niacin therapy but not after thiamine administration Despite these interesting reports it is uncertain whether significant cardiac dysfunction may result specifically from pellagra

Other Vitamin Deficiencies

Cardiac disease has been attributed to a

lack of vitamin C (ascorbic acid) on the basis of experimental studies Deficiency of ascorbic acid has been especially related to the development of rheumatic fever and rheumatic heart disease [18, 213, 1] There has been no acceptable support for these relationships in humans Hemorrhagic pericardial effusions have been reported in severe cases of scurvy [98] as part of the hemorrhagic tendency Erdheim [95] described the occurrence of cardiac hypertrophy in children dying of scurvy and referred to the enlarged heart as "Barlow Herz In the absence of adequate clinical data the possibility that he was dealing with associated beriberi heart disease cannot be excluded

Cardiac disease due to vitamin D deficiency was reported by Meixner [212] Here too it is probable that the changes described were due to associated thiamine deficiency

On the other hand *excessive vitamin D* ingestion has resulted in metastatic calcification with gross and microscopic calcific deposits in arterial media myocardium and cardiac valves [200]

GLYCOGEN CARDIOMEGALY (See also p 786)

These are cases in which excessive glycogen storage in the heart leads to an increase in the size and weight of that organ [2, 6, 2, 8] Clinically they present the problem of cardiac enlargement and heart failure Sudden death may occur [7] without apparent cause (p 786) Pathologically they have been mistakenly incorporated in the motley group of cases of idiopathic hypertrophy of the heart Rhabdomyomata of the heart have been interpreted as glycogen rich muscle fiber accumulations representing a local form of von Gierke s disease (p 1070)

XANTHOMATOSIS AND HYPERCHOLESTEROLEMIA

Xanthomatosis is an hereditary disorder of lipid metabolism characterized by (1) yellowish plaques and nodules (xanthoma) over the elbows knees buttocks and over the tendons and joints of the fingers toes wrists and ankles and also xanthelasma of the eyelids (2) hypercholesterolemia (p 425) and possibly (3) xanthomatous biliary cirrhosis [34]

This type of primary xanthomatosis (xanthomatosis tuberosa) which is associated with an elevated serum cholesterol is of great cardiologic interest because of the frequency of angina pectoris coronary occlusion and sudden death in families subject to this metabolic disorder [232, 233] Intermittent claudication, due to involvement of the vessels of the extremities, may also occur However, hypertension is unusual

A characteristic feature is the early age at which these serious complications often appear [31] Thus Bloom Kaufman and Stevens[229] reported that of [redacted] children of a single family affected by this disease 4 died suddenly between the ages of 6 and 23 years, the cause of death being attributable to xanthomatous lesions in the cardiovascular system Observations at necropsy in one of the fatal cases, in which death occurred at 23 years of age showed advanced atheromatosis of the aorta and coronary arteries and myocardial degeneration of the heart Typical foam cells were seen in the microscopic lesions of the aorta

The hypercholesterolemia is of interest because of the possible relationship to the development of atherosclerosis (p 425) Hypercholesterolemia without cutaneous lesions may be found in some members of families with xanthomatosis [230] This suggests that the elevated serum cholesterol is the fundamental manifestation of the metabolic disorder [235] According to Wilkinson et al [35] the disease is inherited as an incomplete dominant xanthoma tuberosum representing the homozygous and hypercholesterolemia with xanthelasma the heterozygous abnormal The increase in blood cholesterol is endogenous, not dietary and [redacted] influenced little if at all by restriction of cholesterol intake

The *diagnosis* of familial xanthomatosis of the cardiovascular system should be considered whenever angina pectoris or coronary occlusion occurs among young adults or whenever there are characteristic xanthomatous cutaneous nodules and plaques associated with hypercholesterolemia A careful history may add confirmation by disclosing the occurrence of sudden death in siblings and parents at very early ages Members of the afflicted patient's family should have determinations of the blood cholesterol even if there are no symptoms and cutaneous lesions

ACUTE PORPHYRIA

This disease is characterized by psychic instability abdominal pain and findings resembling ileus flaccid paralyses and porphyrin in the urine with or without photosensitivity Hypertension and renal disease are frequently

associated possibly due to the arteriospasm of the general disease Goldman and Kaplan [38] reported tachycardia hypertension and T wave changes and degenerative and pigmentary changes in the myocardium *in cases of* acute porphyria Flaser and Kondo [37] reported elevations of the RT segment in lead I diminished voltage of the QRS and left axis deviation These changes disappeared during the period of remission The authors suggested that the electrocardiographic changes were due to *transient angiospasm* in acute porphyria which involved the coronary arteries as well as other blood vessels However, Crouch and Herrmann [illegible] found normal electrocardiograms in [illegible] patients with acute porphyria

GOUT

Although there is a tendency to hyperuricemia in the young individual with coronary *atherosclerosis* (p 116), the uricemia of gout has not been shown to contribute *to the de*velopment of atherosclerosis Neither is there evidence that the patient with gout is abnormally susceptible to clinical coronary *atherosclerosis* But uric acid crystals may be found in the heart muscle, cardiac valves or blood vessels *as in the* two cases reported by Traut et al [41] A tophus of the mitral valve *in* gout was reported by Bunim and McEwen [39] Cure of heart block in a patient with gout by the administration of Benemid was *attributed* to elimination of a gouty tophus in the conduction system [40]

HYPERSEROTONINEMIA

Serotonin (5 hydroxytryptamine) a product of tryptophan metabolism is produced in excessive quantities *and released* into the *blood stream* by a carcinoid of the small intestine with metastases to the liver *The serotoninemia* may be *responsible for* lesions of the pulmonic and tricuspid valves (pulmonic stenosis and tricuspid insufficiency) congestive heart failure with edema, as well as for distinctive irregular flushing telangiectasia mottled cyanosis diarrhea and asthma like symptoms [44, [illegible], 42, 45, 47, [illegible]] A simple diagnostic test has been devised based on the urinary excretion of 5 hydroxyindoleacetic *acid (5HIAA)* [46]

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Chapter 43

THE HEART AND CIRCULATION IN ANEMIA

Anemia may affect the heart by direct impairment of its oxygen supply or by increasing its mechanical load through the alteration of its circulatory dynamics. When severe anemia develops acutely from rapid and profuse blood loss, symptoms of shock may dominate the picture not because of anemia but because of an insufficient cardiac output due to a deficient blood volume.

Anemia and Preexisting Heart Disease

Intense chronic anemia produces anatomic and physiologic disturbances as a rule only when the heart is already diseased, but occasional instances of failure of a normal heart purportedly due to anemia alone have been reported.[4] Anemia is particularly likely to cause serious anoxia in the myocardium which is already predisposed by severe coronary atherosclerosis or in the enlarged rheumatic heart with its exaggerated need for oxygen.

I have repeatedly observed in patients with atherosclerotic or rheumatic heart disease the precipitation of heart failure and/or coronary insufficiency by severe anemia due to a bleeding peptic ulcer or hiatus hernia, or occasionally due to a bleeding colonic or gastric neoplasm, bleeding hemorrhoids, ulcerative colitis or a hemolytic crisis.[9, 31] In such cases elevation of the level of hemoglobin is often the only effective method of eliminating the cardiac and circulatory symptoms. Care should be employed not to precipitate acute pulmonary edema by too rapid or too large transfusions of blood.[10] The use of concentrated red blood cells with minimal plasma is preferable to that of whole blood if the deficiency is due entirely to the anemia and not to inadequate blood volume. The patient should be propped up in bed during the transfusion to reduce the possibility of inducing pulmonary edema. Repeated determinations of vital capacity and venous pressure may disclose impending or actual overhydration of the lungs or subcutaneous tissues before they are discovered by physical examination.[9]

Degree of Anemia. Contrast between Chronic Anemia and Acute Hemorrhage

As a rule cardiac manifestations and circulatory disturbances appear in chronic anemias only when the anemia is very severe. According to Brannon, Merrill and associates,[11] serious disturbances did not usually occur in their patients until the hemoglobin fell below 7 gm per 100 cc, but moderate circulatory abnormalities appeared when the hemoglobin level was between 8 and 8 gm. The circulatory abnormalities result exclusively from the deficient oxygen content of the blood and are recounted below.

In acute hemorrhage the problem is quite different and relates to the reduction in circulating blood volume and the physiologic compensations to that reduction. Loss of about 500 cc of blood results in slight tachycardia, a slight fall in atrial pressure and little or no reduction in cardiac output.[15, 18] Occasionally a fall in blood pressure and collapse result from reflex vasodilatation and a consequent drop in peripheral resistance. But with more profuse rapid blood loss (1000 cc or more) the blood volume is reduced, the cardiac output is sharply diminished and the arterial blood pressure falls.[12] The clinical picture of shock develops concomitantly with intense sympathetic vasoconstriction. Later as hemodilution occurs the physiologic disturbances are complicated by those due to the anemia itself (infra).

Etiologic Types of Chronic Anemia and Circulatory Disturbance

The cardiac and circulatory disturbances are essentially identical whatever the cause of the anemia, so long as it is severe. As a rule these disturbances occur in chronic anemias for which there is no satisfactory treatment and in anemias with uncontrollable recurrent hemolytic crises. But they may also develop in curable anemias which remain untreated be-

cause of lack of facilities or ignorance on the part of the patient

In former years the anemia known as chlorosis commonly produced cardiac manifestations[4] but this anemia possibly nutritional in origin has mysteriously disappeared or has been absorbed under other classifications Pernicious anemia was long the common type of anemia associated with cardiovascular disturbances[17] [1] The discovery and wide spread use of B_{12} therapy has minimized the frequency of prolonged anemia of this kind At present sickle cell anemia is a frequent cause of cardiac and circulatory abnormalities because of the intensity of the anemia (the red blood counts are usually between 1 000 000 and 3 000 000 or less) and because of its relative chronicity and unsatisfactory response to treatment[5] Of interest also are the cases of intense chronic anemia with cardiac disturbances due to hookworm anemia studied and reported by Porter[43] Gelfand[**] called attention to the frequency of very severe anemias and consequent cardiac disability in tropical areas where medical attention is long delayed Among 42 cases of heart disease treated in a native hospital there were 7 with congestive heart failure due to anemia The hemoglobins in these patients had fallen to between 10 and 20 per cent before hospitalization

PATHOLOGIC PHYSIOLOGY

A sharp reduction in the hemoglobin and therefore in the oxygen transport power of the blood tends to produce relative tissue anoxia This deficiency is compensated by a variety of physiologic adjustments which restore an adequate oxygen supply to the tissues Remarkable as these compensations are they draw upon the circulatory reserves even when the patient is at rest In consequence despite severe anemia an adequate circulation becomes available when the patient is at rest but little or no further reserve is available to meet the demands of physical exertion or other circulatory strains Under the latter circumstances neither the heart nor other tissues may receive an adequate supply of oxygen and the patient may suffer from dyspnea weakness angina pectoris or swelling of the legs But as a rule the following circulatory compensations maintain the patient free of symptoms during ordinary activities despite severe anemia

Circulation Speed

This is accelerated in cases of severe anemia as demonstrated by Blumgart et al[8] by means of radium C I have frequently found the circulation time (calcium gluconate) in patients with hemoglobins between 6 and 8 gm to vary between 8 and 10 seconds whereas the normal circulation time varied between 12 and 13 seconds In general, the velocity of blood flow increases in proportion to the degree of anemia[49] [52] The circulation speed is not noticeably affected until the hemoglobin falls below 9 gm or the red blood count below 3 000 000 per cc, pronounced acceleration occurs only after the hemoglobin level is less than 7 gm[8] Because of the increased velocity of the circulation the quantity of blood passing through the tissues in a given time may be increased 100 per cent or more This permits the tissues to abstract as much oxygen in a unit of time as they would if the hemoglobin content were normal The findings with the venous occlusion plethysmographic method provide quantitative measurements of the increased blood flow through peripheral tissues[1]

The *mechanism* by which the circulation speed is increased is probably a peripheral one The tissue anoxia which develops with the onset of severe anemia leads to the accumulation of acid metabolites which by direct local or reflex action cause peripheral vasodilatation This concept is supported by the finding of greatly diminished peripheral resistance in severe chronic anemia[49] [11] [**] Such vasodilatation permits a more rapid venous return to the heart as if there were multiple peripheral arteriovenous shunts Analogous mechanisms account for the rapid circulation rate of arteriovenous fistula hyperthyroidism beriberi and pregnancy In addition to this effect the factor of diminished viscosity due to the low red blood count contributes significantly to the acceleration of circulation

In cases of intense chronic anemia complicated by congestive *heart failure the circulation* speed may be normal The slowing effect of heart failure neutralizes the acceleration due to anemia the exact resultant depends on the degree of each In the presence of congestive heart failure the finding of a normal circulation time should suggest the possibility of an associated severe anemia as well as other conditions which increase the velocity of blood flow

Oxygen Utilization

Compensation for deficient oxygen content of the blood due to severe anemia may be effected not only by an increased speed of circulation but also theoretically, by a more complete abstraction of oxygen from the blood by the tissues Actually the absolute oxygen utilization per unit of blood is diminished, i e the arteriovenous oxygen difference is less than normal [11, 45] But relative to the amount of hemoglobin oxygen available, the percentage of oxygen utilization is enhanced Normally the arterial oxygen content reaching the tissues is 19 volumes per cent and the venous oxygen content leaving the tissues is about 14 volumes per cent Therefore 5 volumes per cent of oxygen have been abstracted or 5/19 (26 per cent) of the arterial oxygen In a patient with 6 gm per 100 cc of hemoglobin the arterial oyxgen content is about 8 volumes per cent whereas the venous oxygen content may be 5 volumes per cent The absolute arteriovenous oxygen difference is 3 volumes per cent which is less than normal but the percentage of available oxygen utilized is 3/8 (37 5 per cent) which is more than normal The reduction in arteriovenous oxygen difference (i e , the absolute quantity of oxygen abstracted from a unit of blood) may be due, among other factors, to the speed with which the blood rushes past the tissues

The arterial oxygen saturation may be normal or reduced [44] There is evidence of a significant increase in the alveolar arterial gradient with a reduction in arterial oxygen tension [46]

Cardiac Output (Minute Volume)

That the cardiac output is greatly augmented in cases of severe anemia was demonstrated by Richards and Strauss[45] and Stewart et al ,[49] among others Similar findings were more recently noted by the direct Fick method catheterization of the heart being employed to obtain mixed venous blood [43, 11] Brannon Merrill and associates[11] found the cardiac index to be 6 5 (liters per sq meter body surface area) when the hemoglobin level averaged below 5 gm , 4 7 when the hemoglobin ranged between 5 and 7 gm 4 0 when the hemoglobin was between 7 and 9 gm and 3 1 or about normal when it ranged between 9 and 13 gm Not only is the cardiac output augmented, but also there may be excessive increase in response to exercise [54]

The increased cardiac output results essentially or exclusively from the accelerated speed of the circulation and the consequently augmented venous return To a variable extent the increase in minute volume is mediated by an *increase in the cardiac rate* but the stroke output is also substantially elevated Following transfusions and consequent increase in the hemoglobin level, the circulation speed diminishes and the cardiac output falls When severe chronic anemia is complicated by congestive heart failure, the cardiac output may nevertheless substantially exceed the normal (high output failure) Presumably, although the cardiac output is above normal, it is deficient relative to the needs of the tissues

The *work of the heart* may not be increased despite the augmented cardiac output, according to the studies of Stewart, Crane and Deitrick[49] in 5 cases of pernicious anemia Owing to peripheral vasodilatation the peripheral resistance is greatly diminished and the blood pressure is moderately lowered[4] Peripheral vasodilatation i e diminution in peripheral resistance, is not uniform throughout the tissues Whereas the cerebral, coronary and skeletal muscle blood flow[29] is increased owing to diminished peripheral resistance, the renal[10] and cutaneous blood flow is reduced Studies of varying degrees of anemia induced in the open chest dog disclosed an increased coronary flow per unit of left ventricular work [16] Decreased oxygen carrying capacity was largely compensated by an increased coronary flow resulting from a diminished coronary resistance The work of the heart is proportional to the cardiac output and the mean arterial pressure, the reduction in blood pressure with severe anemia may largely neutralize the effect of the increased cardiac output The fall in viscosity likewise diminishes the work of the heart

There is no evidence that the deleterious effect of anemia on the heart is due to the mechanical strain of an increased cardiac output It is more probable that the heart suffers directly because of anoxia when the limits of coronary dilatation are reached with severe anemia, no further increase in coronary blood flow is then possible to compensate for the extreme reduction in oxygen capacity of the anemic blood Compensation may then be effected only by cardiac dilatation and hypertrophy In the presence of coronary stenosis the ability to increase the coronary flow required to compensate for anemia is greatly restricted

The Circulating Blood Volume

The blood volume in anemia is slightly diminished chiefly due to the reduction in the number of erythrocytes (low hematocrit [5]) The plasma volume may be normal but often it is elevated [9] Since the total blood volume is diminished or normal it is apparent that the augmented venous return and cardiac output in severe anemia result exclusively from the increased speed of circulation In cases of severe anemia complicated by congestive heart failure the plasma volume may be greatly increased even to the point of causing an increase in total blood volume [9] This increase may be viewed as a compensatory mechanism utilized to maintain the cardiac output at required levels

The *blood pressure* tends to depression of both the systolic and diastolic levels but especially of the latter The pulse pressure tends to increase [5]

The *venous pressure* is not elevated when the patient is at rest in the absence of congestive heart failure

The *vital capacity* of the lungs is diminished The respiratory minute volume and residual air are increased [7] The explanation for this is uncertain An increased blood flow through the lungs has been held responsible but this explanation is unclear

PATHOLOGY

Severe longstanding anemia is associated with cardiac dilatation and hypertrophy (see below) In cases of anemia due to acute hemorrhage the musculature is usually firm in cases of chronic anemia the musculature is flaccid

Fatty degeneration of the heart muscle is characteristic of intense chronic anemia It is distributed in a striking fashion perpendicular to the fibers of the trabeculae and papillary muscles producing the yellow streaking known as *tigering of the heart* The fatty change is presumed to result from disturbances in cellular metabolism due to oxygen deficiency While fatty degeneration of the myocardium is characteristic of severe anemia it may also be caused by a variety of infectious processes and toxic substances as well as extensive severe coronary artery disease

Of special interest are the changes in the heart observed in instances of intense anemia due to gastrointestinal bleeding in young individuals In such cases I have observed diffuse focal or confluent areas of myocardial necrosis chiefly in the subendocardial myocardium of the left ventricle and especially of the papillary muscles [21] The coronary arteries may be normal The subendocardial regions have the poorest blood supply and suffer most from anoxia when there is a reduction in blood flow or in the oxygen content of the blood Similar subendocardial necroses have been produced experimentally in rabbits by bleeding [13]

CLINICAL FEATURES RELATED TO THE CIRCULATION IN ANEMIA

Severe anemia and the compensatory mechanisms which it invokes are responsible for a variety of clinical manifestations referable to the cardiovascular system These may closely simulate the symptoms and signs usually due to organic heart disease It is not uncommon for heart disease and heart failure to be diagnosed because of such manifestations due entirely to anemia alone On the other hand severe anemia may precipitate or intensify heart failure or coronary insufficiency in the presence of preexisting cardiac or coronary disease For this reason it is often necessary to correct the anemia by transfusion or specific therapy in order to evaluate the extent to which anemia is partly or entirely responsible for the symptoms In this connection it is well to recall that anemias of nutritional origin may be associated also with vitamin B deficiency and that the latter may also contribute to the development of cardiovascular symptoms (p 1037)

Cardiac Enlargement

The outstanding cardiac manifestation of severe chronic anemia is enlargement of the heart This was demonstrated experimentally in dogs rendered anemic by bleeding [15] Cabot and Richardson[13] reported significant cardiac hypertrophy in 18 of 19 hearts of patients who had died of pernicious anemia In one case the heart weight was 710 gm The possibility of concomitant cardiovascular disease contributing to the development of the hypertrophy may be properly considered in such cases since insufficient data are presented to evaluate the care with which the coronary arteries were studied at that time (1908 to 1919)

The most impressive evidence of cardiac enlargement in severe anemia is presented by roentgenologic observations (Fig 157A) Ball[3] demonstrated by serial films that the cardiac

enlargement associated with anemia disappeared following relief of the anemia (Fig 157*B*) Porter[43] observed cardiac enlargement regularly in his cases of severe anemia due to hookworm infestation In most of these the enlargement was reversible, as demonstrated by a reduction in the size of the cardiac silhouette following therapy But in longstanding cases the size of the heart remained unaltered an observation which led Porter to conclude that the enlargement in these cases

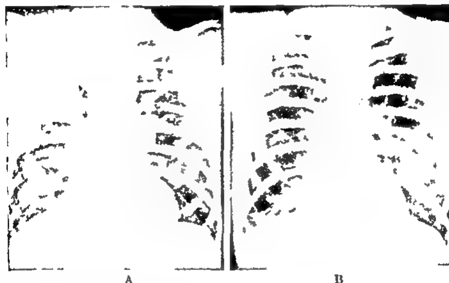


Fig 157 *A* Generalized cardiac enlargement associated with anemia probably due to sulfonamides given for pneumonia of right upper lobe
B Recession of cardiac silhouette to normal in three weeks as anemia was corrected

was due to hypertrophy Ellis and Faulkner[19] noted cardiac enlargement by roentgenologic examination in 20 of 38 cases of anemia The incidence of enlargement was greater in the group with hemoglobins below 50 per cent than in the group with hemoglobins above that level Regression of enlargement followed elevation of the hemoglobin by appropriate treatment Usually the cardiac silhouette reverted to normal size in three to twelve weeks

The *mechanism of cardiac enlargement* in anemia is uncertain That the work of the heart may not be significantly enhanced has already been mentioned (p 1048) But further investigations in cases of very intense anemia may disclose a greater work strain than in the small series of cases studied by Stewart and his associates [illegible] By exclusion it appears likely that the enlargement is due to the direct effect of anemia on the heart This may result in myocardial inefficiency due to anoxia with a tendency to reduction in the cardiac output The accumulation of blood in the chambers results in stretching of the fibers (dilatation), more forceful contraction and restoration of the needed output (p 86) When an adequate cardiac output cannot be maintained by means of this dilatation (and perhaps subsequent hypertrophy) other compensatory mechanisms are invoked which eventually lead to the clinical syndrome of heart failure

Cardiac Murmurs

The occurrence of cardiac murmurs in anemia has long been common knowledge Anemia is the classic cause of the so-called functional cardiac murmur The murmur associated with anemia is almost always systolic in time and heard either over the pulmonic area in the second or third interspace to the left of the sternum or in the apical region [illegible] The murmur may be audible throughout the precordium but then it is usually loudest in one of these two areas Occasionally the systolic murmur is heard best over the aortic area Radiation of apical systolic murmurs to the axilla or back in children has been described by Parsons and Wright[39]

Of greater interest is the occasional appearance of a diastolic murmur in patients with anemia but without organic heart disease [illegible] Such functional diastolic murmurs were heard in 6 of 39 patients with pernicious anemia studied by Goldstein and Boas[4] The diastolic murmur has a blowing quality and may occur early in diastole and be localized to the left

border of the sternum like the murmur of aortic insufficiency But late diastolic or presystolic murmurs have also been described which are heard best at the apex and simulate the murmur of mitral stenosis[24, 6] Despite the above mentioned figures, it should be emphasized that diastolic murmurs are relatively rare in cases of anemia and have been heard only when the anemia is extremely intense and chronic as in cases of sickle cell anemia and formerly in cases of pernicious anemia before specific therapy was available Even in such cases the impression of a diastolic murmur may be created by a presystolic gallop or by a booming first sound as in hyperthyroidism

The systolic murmurs heard in cases of anemia have been attributed to the speed of the blood flow and to dilatation of the ventricular chambers and atrioventricular rings Diastolic murmurs have been explained as being due to dilatation of the pulmonic or aortic rings and to incomplete opening of the mitral valve associated with flaccidity of the papillary muscle[40] When severe anemia is associated with greatly increased flood flow diastolic murmurs may be due to functional stenosis of the mitral or tricuspid valve Both systolic and diastolic murmurs are variable in occurrence appearing and disappearing with intensification or relief of the anemia respectively

Electrocardiographic Changes in Anemia

Many observers have reported no significant electrocardiographic changes[54] but others have reported consistent changes when the anemia is very intense[51, 6] The common abnormalities are[40] depression of the ST segments and flattening or inversion of the T waves findings suggestive of myocardial anoxia Similar ST deviations and alterations of the T wave attributed to coronary insufficiency have been observed after an acute loss of blood[47, 37] Occasionally low voltage of the QRS complexes and prolongation of the P R interval have been observed in cases of chronic anemia

The electrocardiographic abnormalities usually disappear when the anemia is relieved[19]

Heart Failure in Anemia

Dyspnea on exertion tachycardia and palpitation edema of the legs and cardiac enlargement occur commonly in severe chronic anemia and the combination of these symptoms and signs may be the basis of a mistaken diagnosis of congestive heart failure Enlargement of the liver as in cases of sickle cell anemia may add to the resemblance The absence of orthopnea pulmonary congestion and venous engorgement and the finding of a normal venous pressure are the bases for excluding heart failure as the cause of the exertional dyspnea and the subcutaneous edema

More study is desirable to illuminate the mechanism by which the various circulatory symptoms are initiated Breathlessness occurs as a rule only with exertion It may be that there is no pulmonary congestion at rest but that it appears during exercise because the left ventricle is unable to handle the increased venous return Reduced arterial oxygen capacity decreased oxygen saturation of the blood during effort and accumulation of blood lactic acid[7] may be contributory factors

The cause of the edema is also obscure since it may be present despite a normal venous pressure Possibly edema develops because of recurrent transient elevations of venous pressure following physical exertion during the course of the day Hypoproteinemia may be a contributory factor in some cases But Strauss and Fox[50] found no relation between edema and the plasma protein in their anemic patients The degree of water retention and visible edema following salt ingestion in their cases varied inversely with the hemoglobin level The venous pressure was normal before salt administration but no mention is made of venous pressures following the ingestion of salt and the appearance of edema Increased capillary permeability due to anoxia has also been suggested as a cause of edema in cases of anemia but it is doubtful whether the degree of anoxia is sufficient to affect vascular permeability Henry et al[37] found evidence of increased capillary permeability as indicated by protein in capillary filtrate after venous occlusion of an extremity but only when there was severe local anoxia as indicated by an oxygen saturation of the venous blood of 15 to 25 per cent or less Comparable low oxygen contents of the venous blood occur in cases of severe anemia but it is questionable whether these observations following venous occlusion can be applied to cases of anemia

But actual heart failure may complicate severe anemia Then dyspnea may occur at rest or on slight exertion orthopnea or cardiac asthma appear occasionally Rales at the bases of the lungs hepatic enlargement and tenderness subcutaneous edema, engorgement

of the superficial veins and elevation of the venous pressure may all be present In such cases it is a good rule to consider the likelihood that there is underlying cardiac disease although heart failure due to uncomplicated anemia has been noted

Angina Pectoris and Anemia (See also p 452)

Angina pectoris has been observed with varying frequency in reported series of cases of severe anemia [54, 41, 3] Pain of cardiac origin has been attributed to the lower oxygen content of the anemic blood Intermittent claudication of the lower extremities, observed by Pickering and Wayne[41] in some extremely anemic patients was attributed to similar anoxia of the calf muscles The relation of anemia to angina pectoris has been discussed above (p 1046) It appears likely that anemia is only a contributory factor in the production of angina pectoris usually in patients with underlying severe coronary atherosclerosis However angina pectoris attributed to anemia per se has been reported [13]

THE HEART IN SICKLE CELL ANEMIA

The described cardiovascular disturbances may occur in any longstanding intense anemia But sickle cell anemia merits special discussion because

(1) It is probably the commonest form of anemia observed today in which the degree of anemia is intense enough and of sufficient duration to produce cardiac symptoms,

(2) It is frequently complicated by symptoms which lead to a mistaken diagnosis of rheumatic fever rheumatic or congenital heart disease or subacute bacterial endocarditis

(3) It is occasionally associated with disseminated occlusions of the small pulmonary arteries which may result in pulmonary hypertension and chronic cor pulmonale[56, 3, 55] (p 982)

The occurrence and frequency of cardiac manifestations in sickle cell anemia have been discussed by Anderson and Ware,[2] Klinefelter,[32] Winsor and Burch[55] and by Grover [5] among others Winsor and Burch reported that 40 patients with heart disease due to sickle cell anemia were admitted to the Charity Hospital New Orleans in a single year and that heart disease due to this cause was more frequent among their Negro patients than that due to beriberi myxedema, pernicious anemia or trauma

Hemodynamic studies[24] have disclosed a high cardiac output and frequent reduction in arterial oxygen saturation, with a fall in oxygen saturation during exercise in many cases

Significant cardiac enlargement was present in at least 75 per cent of the cases of sickle cell anemia observed by Anderson and Ware and in 95 per cent of those studied by Winsor and Burch [55] Both the left and right ventricles are usually enlarged The pulmonary salient of the cardiac silhouette is often prominent and the left border is straightened but the left atrium is not enlarged [2, 55] Cardiac murmurs are heard in almost all cases Most often they are systolic in type and heard over the mitral or pulmonary areas but systolic murmurs may be audible over any part of the precordium Occasionally a diastolic murmur may also be audible over the mitral, aortic or pulmonic regions The second pulmonic sound is often accentuated and may be split Dyspnea is common but orthopnea and cardiac pain are rare Hepatomegaly occurs frequently either as an intrinsic element of the disease or due to chronic passive congestion Pulmonary infarction, pulmonary occlusion of the small arteries and pulmonary endarteritis and pulmonary edema occur frequently Electrocardiographic abnormalities are non specific and inconstant Right axis deviation is rare despite the frequency of right ventricular dilatation and hypertrophy Circulatory deaths are frequent owing to the sensitivity of patients with sickle cell anemia to anoxemia and shock, anesthesia and surgical procedures infection and loss of blood

Of special importance is the frequency with which cardiac findings due to sickle cell anemia are interpreted as being due to rheumatic or congenital heart disease [3] There are several reasons for this error Sickle cell anemia is the commonest reported cause of a functional diastolic murmur Even when there is only a systolic murmur organic heart disease is usually suspected because almost always significant cardiac enlargement is associated An apical systolic murmur, often radiating to the axilla an accentuated second pulmonic sound and cardiac enlargement with straightening of the left border of the heart on fluoroscopic examination strongly suggest rheumatic mitral valvular disease This diagnosis seems to be supported by the history of attacks of pain in the extremities especially about the joints which may be warm and swollen In

addition, fever is common during these attacks and leukocytosis is usual as in other hemolytic anemias During the acute attacks of pain and fever the finding of cardiac murmurs suggests that the above symptoms are due to recurrent acute rheumatic fever Occasionally a diagnosis of subacute bacterial endocarditis is made because of the combination of fever with a cardiovalvular lesion Occasionally, because of the youth of the patient with sickle cell anemia and because of the absence of a history of rheumatic fever a diagnosis of congenital heart disease is made

Diagnosis and Differential Diagnosis of Sickle Cell Anemia and Heart Disease

The possibility of sickle cell anemia should always be investigated in any young Negro suspected of having organic heart disease Sickling of the red blood cells should be sought also if cardiac murmurs and enlargement are discovered in any patient with a red blood count of less than 3 500 000 or a hemoglobin of less than 10 gm Differentiation from rheumatic mitral disease may be aided by the absence of left atrial enlargement in sickle cell anemia even when the pulmonary salient is prominent and by the usual absence of right axis deviation Salicylates are unlikely to relieve the joint pains and swelling The finding of ulcers or the scars of ulcers near the ankles should also suggest sickle cell anemia in young colored individuals suspected of heart disease The coexistence of rheumatic heart disease and sickle cell anemia has been described[4] and this possibility should be carefully considered

LEUKEMIA

Leukemic infiltrations of the heart were found in 43 of 123 fatal cases of leukemia [59] In chronic forms of leukemia associated with severe anemia cardiac enlargement systolic murmurs tachycardia and palpitation exertional dyspnea and subcutaneous edema may occur as in any other type of anemia Occasionally there is frank evidence of congestive heart failure [57] In such cases a diagnosis of heart disease and heart failure is usually made without recognition of the causative leukemia

Electrocardiographic changes in cases of leukemic infiltration of the heart include sinus tachycardia ST segment depression T wave inversion in limb and precordial leads prolongation of the P R interval and premature contractions [57]

Leukemic infiltrations of the pericardium with pericardial effusion which is often hemorrhagic have been described [illegible] Roentgen ray therapy in a patient with heart block presumably due to leukemic infiltrations resulted in temporary disappearance of the conduction defect [58]

CARBON MONOXIDE POISONING

Carbon monoxide poisoning like anemia, reduces the oxygen transport capacity of the blood In addition the formation of carboxyhemoglobin may interfere with the dissociation of the remaining oxyhemoglobin Cardiac damage results from myocardial anoxia and depends on the severity and duration of the carboxyhemoglobinemia Direct toxic damage to the heart muscle has also been claimed [62] Concentrations of 25 to 35 volumes per cent of carbon monoxide in the blood are necessary before clinical manifestations appear The importance of carbon monoxide poisoning as an industrial and domestic hazard is indicated by its position second in frequency only to auto injuries as a cause of accidental and suicidal death

Clinical manifestations are most commonly referable to the central nervous system but our interest here lies particularly in the cardiac symptoms due to carbon monoxide poisoning Such neurologic and cardiac symptoms may arise from prolonged exposure to concentrations of 0 01 to 0 02 per cent of carbon monoxide or they may represent the residua or sequelae from acute asphyxia due to exposure to much higher concentrations of the gas It has been emphasized that chronic disease of the nervous system and heart may develop even when there is no loss of consciousness from the intoxication

Experimental carbon monoxide poisoning of animals has resulted in vascular lesions consisting of small hemorrhages and perivascular infiltrations as well as focal areas of necrosis in the heart [illegible, 76, illegible] Similar myocardial necrosis has been observed in humans who have succumbed following carbon monoxide intoxication [73, 68, 70, 61] The lesions in the heart are confined essentially to the left ventricle and papillary muscle and more particularly to the subendocardial region These lesions resemble those observed following prolonged coronary insufficiency without coronary occlusion [55, 57] Coronary thrombosis following petrol-exhaust gas was reported by Hadley [illegible] and rupture of

the heart following coal gas poisoning by Pulvertaft.[74] In some of the reported cases which concern older individuals it is difficult to apportion the relative influence of preexisting coronary atherosclerosis and of carbon monoxide in the production of myocardial lesions.

Clinical evidence of myocardial involvement may appear promptly or several days after the acute intoxication by carbon monoxide. Or it may appear gradually after *prolonged or repeated exposure*. The chief symptoms are angina pectoris and cardiac irregularity.[64, 71, 7] Palpitation, tachycardia, precordial oppression or pain, exertional dyspnea and weakness have been noted. An attack of acute coronary occlusion has been attributed to carbon monoxide poisoning.[6] Atrial fibrillation may be precipitated. When cardiac enlargement is observed, the presence of some preexisting cardiovascular abnormality is likely. *The relative importance of such* underlying disease as the cause of the patient's cardiac symptoms and signs may present a medicolegal problem if the patient attempts to collect insurance, compensation or personal damages following carbon monoxide poisoning. As a rule, symptomatic recovery from the cardiac disturbances is complete within a few weeks or months but chronic organic heart disease may result from carbon monoxide intoxication according to Beck and Suter.[6]

Electrocardiographic changes have been repeatedly observed but they may be absent even when the carbon monoxide poisoning is severe enough to be fatal.[74, 77] The most frequent abnormalities are slight ST interval depressions and lowering or flattening, rarely inversion, of the T waves, the so-called pattern of coronary insufficiency.[77] Paroxysmal atrial fibrillation and premature beats are not rare. Occasionally lowering of the voltage of the QRS complexes, intraventricular block or prolongation of the P-R interval has been observed. As a rule the electrocardiogram reverts to normal within two months, but occasionally the abnormalities persist.

POLYCYTHEMIA

Polycythemia (erythremia) may be a consequence or a cause of cardiovascular disease. Polycythemia is a characteristic finding with certain congenital cardiac lesions such as the tetralogy of Fallot, in which there is a large venous-arterial shunt. It is also observed in cases of severe chronic pulmonary heart disease (Ayerza's syndrome) and not infrequently in cases of very severe chronic heart failure such as that associated with tricuspid stenosis (p. 714). In the presence of polycythemia, the possibility of these causative forms of heart disease should be considered. In all of these examples the polycythemia is viewed as a compensatory response to a sharp reduction in the oxygen saturation of the arterial blood.

Polycythemia, Vascular Thromboses and Coronary Disease

Polycythemia is frequently complicated by circulatory disturbances due to increased viscosity and slowing of the blood. Arterial and venous thromboses occur particularly in the cerebral and peripheral vessels.[85] Not infrequently also, polycythemia is associated with thrombosis of a coronary artery and myocardial infarction. It is likely that in such instances the polycythemia is a contributory cause and not merely coincidental with the coronary occlusion. The occurrence of coronary thrombosis in cases of polycythemia vera has been documented by Christian,[81] Oppenheimer,[87] Boyd[79] and by Dameshek and Henstell[8] among others. Tinney, Hall and Giffin[83] found clinical evidence of coronary disease in 10 (6 per cent) of 163 cases of polycythemia vera. Four of these patients with coronary disease had angina pectoris. One of these, a woman 48 years old, suffered a coronary occlusion in the absence of hypertension or diabetes.

Polycythemia and Absence of Heart Failure

Polycythemia is associated with a greatly augmented blood volume which might be considered to produce an unusual load on the heart and congestion of the viscera. Nevertheless, heart failure is a rare complication except when there is associated myocardial infarction or hypertensive and atherosclerotic heart disease. The increased blood volume is due essentially or exclusively to the increased cell volume and there is a consequent increase in viscosity and a corresponding slowing of the blood stream. The venous return and cardiac output are normal[85, 84] since the effect of the increased blood volume on the venous return is neutralized by the slowing of the circulation. The work of the heart is unaltered except when there is *hypertension*. Similarly cardiac enlargement is notably absent when there are no complications.[80]

Polycythemia and Hypertension

The combination of polycythemia vera and hypertension has been segregated as [redacted] separate syndrome[83] but it [redacted] more probable that the hypertension is [redacted] coincidental abnormality Brown and Giffin[80] found the average blood pressure in 14 cases of polycythemia vera to be 138 mm Hg systolic and 90 diastolic Tinney and his associates[88] found the systolic blood pressure above 150 mm Hg in about 40 per cent and above 180 in about 10 per cent of their 163 cases of polycythemia vera It is uncertain whether these blood pressures exceed those to be found in subjects of similar age groups without polycythemia vera

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Chapter 44

TRAUMATIC HEART DISEASE

Traumatic heart disease includes the anatomic lesions and functional disturbances of the heart which result from external injury or from an intense unusual physical exertion. According to the causative mechanism, cardiac trauma may be classified as follows: (1) penetrating lesions of the chest wall, including those involving foreign bodies in the heart; (2) non-penetrating lesions; (3) physical strain. In addition there are instances of so-called spontaneous rupture, perforation or tear of a cardiac structure in which physical strain may be a *significant contributory factor*.

HEART DISEASE DUE TO PENETRATING LESIONS

Since Rehn[83] successfully sutured a stab wound of the human heart in 1896, numerous similar reports have attested to the curability of penetrating cardiac lesions when the diagnosis is made early and proper surgical repair instituted rapidly. In this country interest in penetrating wounds of the heart has been stimulated in great measure by the reports of Bigger,[1] Elkin,[7] Beck[10] and Harken.[29]

In civilian life, penetrating wounds of the heart result usually from stabbing by knife and occasionally from bullet wounds. Other sharp instruments such as the ice pick, stiletto or needle[25] may be responsible. Needle wounds of the heart may occur accidentally or during pericardial aspiration or intracardiac injections of epinephrine.[7] In warfare, penetrating cardiac injuries are usually due to bullet wounds or shell fragments. Penetrating wounds of the heart may result indirectly when shattered glass or splinters perforate the chest wall in auto or plane accidents or when the heart is torn by the sharp ends of broken ribs.

The usual site of entrance of the penetrating object is the precordium, but occasionally cardiac injury results from penetrating wounds elsewhere in the chest wall or even in the neck, abdomen or pelvic region. Of special interest are the lesions associated with *foreign bodies in the heart*[91] such as needles, bullets and shell fragments, which may enter the heart directly or as emboli from a nearby or distal vessel. The foreign body may lodge in a peripheral vein and reach the cardiac chambers by way of the venae cavae or pulmonary veins.[30, 40, 41] Sharp foreign bodies which accidentally reach the esophagus may perforate its wall and thence lacerate *or perforate the heart. McCartney and* Drummond[71] reported a case of gunshot wound of the liver in which the foreign body entered an hepatic vein, reached the right side of the heart and lodged in the right ventricle.

PATHOLOGY

Any portion of the heart may be injured by the penetrating object. Injury to the pericardium alone may give rise to a fibrinous pericarditis or pericarditis with effusion. The concomitant introduction of infectious agents may lead to a purulent pericarditis. The anterior surface of the right ventricle is the most commonly involved portion of the heart, but the right atrium and the left ventricle are also wounded frequently. The intrapericardial portions of the great vessels may be perforated. Traumatic aorto-pulmonary fistula has been reported.[3] Injury to a coronary artery, especially the anterior descending branch of the left coronary, is a common complication of cardiac wounds.[33-38, 99] Although uninjured, the coronary artery may have to be ligated during cardiac suture. Perforation of the myocardium, great vessels or coronary artery is followed usually by hemopericardium. Coronary arterial perforation and thrombosis may be associated with myocardial infarction. The interventricular septum may be injured[19, 26] and the atrio-

ventricular conduction system impaired or interrupted Occasionally, valvular cusps, chordae tendineae or the papillary muscles are perforated or torn with consequent valvular insufficiency and cardiac strain

A ventricular or atrial thrombus may develop at the site of injury or at the site of lodgment of a foreign body Cerebral, pulmonary or peripheral embolization may result from such mural thrombi or from passage of migrating foreign bodies In the majority of cases the foreign bodies lodge in the pericardium or myocardium without further migration Occasionally such a foreign body causes local myocardial injury, hemorrhage and hemopericardium local myocardial abscess or a purulent pericarditis or mediastinitis

CLINICAL FEATURES

The symptoms and signs associated with penetrating lesions of the heart are caused by hemorrhage, acute cardiac tamponade, fibrinous or suppurative pericarditis contusion or infarction of heart muscle valvular rupture or embolism Death may occur suddenly from ventricular fibrillation or ventricular standstill If treatment is delayed death often ensues in a few hours after the injury, due to cardiac compression or exsanguination

Usually the patient when first seen presents some degree of shock from loss of blood, cardiac compression or both He may be stuporous or unconscious confused or delirious Tachycardia a weak rapid pulse, tic tac heart sounds (embryocardia) restlessness and cold moist skin are noted commonly Pallor, a fall in hemoglobin and leukocytosis result from an acute massive loss of blood Sometimes circulatory insufficiency is due not to loss of blood or cardiac compression but to a reflex arteriolar dilatation and consequent reduction in blood pressure [7]

With the rapid development of hemopericardium the heart is compressed, diastolic filling is restricted, the venous inflow is retarded and the cardiac output is sharply curtailed [96] These physiologic disturbances are expressed clinically by a falling blood pressure and pulse pressure, a rising venous pressure, a quiet heart (small excursions fluoroscopically) and a small and paradoxical pulse There may or may not be dyspnea or cyanosis Eventually the frank picture of circulatory shock unfolds Not infrequently the bleeding is moderate and slow and many hours elapse before there is evidence of cardiac tamponade or other signs of cardiac injury There may be a symptom free interval with normal activity prior to circulatory collapse from hemorrhage or cardiac tamponade Sometimes hemopericardium may be delayed for as long as 6 to 22 days after a stab wound to the heart [68]

Pericarditis may be signalled by precordial pain, a friction rub or by signs of pericardial effusion (p 593) If infection develops fever appears and there are progressive signs of cardiac tamponade due to purulent pericarditis

Valvular tears or rupture of the chordae are denoted by loud, rough murmurs and by progressive cardiac insufficiency Injury to a coronary artery usually causes hemorrhage hemopericardium and cardiac tamponade Subsequent spontaneous occlusion or ligation during surgical repair may cause myocardial infarction, sometimes with classic electrocardiographic signs of infarction but without apparent clinical symptoms of that condition

Embolization with resultant hemiplegia pulmonary infarction or acute cor pulmonale or peripheral vascular occlusion and gangrene may result from local mural thrombi at the site of the penetrating lesion or more often from migrating intravascular foreign bodies

Roentgenology

Roentgenologic examination may reveal an enlarged cardiac silhouette due to hemopericardium, but often the hemorrhagic effusion is too small to affect the size of the cardiac shadow The fluoroscopic examination which is of special value discloses an almost complete absence of pulsation during the stage of cardiac tamponade It is also essential for the recognition and localization of intravascular and intracardiac foreign bodies In addition the roentgenologic examination may disclose associated intrathoracic lesions such as fractured ribs hemothorax, pneumothorax and extensive pulmonary hemorrhage

The Electrocardiogram

Electrocardiographic tracings from patients with stab and gunshot wounds of the heart have been published by many authors, but of the most comprehensive reports are those of Wood,[88] Solovay, Rice and Solovay,[88] Herve and Forero and Noth,[75] Kapp and Graham[41] and Biber and Limbeck [11] In the first hours after the injury and before operation there is definite evidence of cardiac involvement in most cases This evidence consists of electro-

cardiographic signs of pericarditis bundle branch block or of myocardial infarction Pre cordial leads may disclose significant abnormalities when none are present in the standard leads[22] However, minor RST deviations and T wave alterations are non specific and may be observed in thoracic wounds without cardiac injury

In the first few postoperative days, the electrocardiogram usually depicts changes associated with pericarditis whatever the site of the wound and whether or not a coronary artery has been injured or ligated during suture A serofibrinous pericarditis is an almost constant sequel of surgical exploration of a cardiac wound There are characteristic RT elevations in leads I and II or in all standard leads As in other forms of pericarditis the elevated RT segment is concave upward while in myocardial infarction it is convex upward

Gradually after one or more weeks the T waves are flattened and later become fully inverted The T wave inversions may persist for many months or years[75] but usually they revert to normal after three months Definite localizing electrocardiographic signs directly due to a left or right ventricular injury may be seen very early before they are masked by the pericarditis or after three or more months when the pericardial signs have disappeared These localizing signs consist of QT patterns similar to those seen with ventricular infarcts or occasionally of evidence of bundle branch block When an injury or suture occludes the anterior descending branch of the left coronary artery there may be a Q_1T_1 pattern due to infarction of the anterior wall of the left ventricle or possibly to a left ventricular wound without coronary artery involvement Multiple precordial leads may reveal localizing signs as evidenced by T wave inversion in one or more leads The important point to emphasize is that electrocardiographic changes represent the most constant evidence of cardiac involvement in penetrating chest wounds their subsidence or persistence may be a reliable index of the functional or organic basis of symptoms which remain for a long time after operation They are less reliable for localization of the exact site of injury

DIAGNOSIS

It is usually simple to diagnose a penetrating wound of the heart if due regard is given to the history of the injury the site of entrance of the penetrating object in the precordial region and the clinical manifestations of cardiac tamponade Greater diagnostic difficulty is encountered when the penetrating object reaches the heart through some point removed from the precordium Then cardiac involvement may be suspected from symptoms and signs of hemopericardium (see pericarditis with effusion p 593 and cardiac compression, p 594) or from loud murmurs a pericardial rub, heart block or congestive heart failure

The association of a stab or gunshot wound of the chest with electrocardiographic changes suggesting myocardial infarction or pericarditis is also diagnostic of cardiac injury The presence of ST and T wave abnormalities following a penetrating chest wound denotes cardiac injury concordant ST elevations and T wave inversions in leads I and II or in all standard leads denote pericarditis not involving the coronary artery, reciprocal ST elevation and depression in leads I and III with inversion of only T_1 or T_3 denote coronary artery injury[6]

It is important to seek and diagnose traumatic lesions associated with that of the heart especially hemothorax hemopneumothorax sucking wounds of the chest and abdominal wounds[79]

In cases of a foreign body in the heart angiocardiographic examination is essential for exact localization[26]

PROGNOSIS AND TREATMENT

Many patients succumb from exsanguination shock and possibly ventricular fibrillation or cardiac standstill before reaching the hospital

Operative intervention was formerly recommended in most cases of penetrating wounds of the heart[27, 8] In recent years there has been a trend toward conservative (non surgical) therapy in most cases[■] In general conservative therapy is maintained when hemorrhage is moderate or slight when there is no evidence of cardiac tamponade or when the signs of tamponade diminish following medical treatment *Pericardial aspiration* is performed promptly for cardiac tamponade and repeated if necessary[8, 9] Operation is indicated when there is severe persistent hemorrhage (free pericardiopleural communication) and when there is evidence of cardiac

tamponade which is not relieved by pericardial aspiration or recurs rapidly after aspiration [87]

When the patient is first seen measures are instituted to counteract hemorrhage and shock Transfusions of compatible whole blood should be given or plasma dextran solution or other fluids may be administered by venoclysis if there is a delay in obtaining whole blood Intravenous infusions may improve the cardiac output and clinical condition even in the presence of cardiac tamponade [21] [86] Norepinephrine should be included in the infusions in the presence of severe hypotension, it may have a favorable effect on the circulation by raising the blood pressure Antibiotics are administered prophylactically A booster dose of tetanus toxoid or tetanus antitoxin is given if indicated The thorax should be examined for the presence of pneumothorax hemothorax or splashing sounds indicative of a free pericardiopleural communication Determinations of the blood pressure and observations of the cervical veins and of the radial pulse should be made during preparations for operation

An anesthetic is usually employed but in cases of extreme urgency if the patient is unconscious and respirations have ceased, the heart may be exposed without anesthesia while artificial respiration is performed If possible the heart is approached extrapleurally through a left anterior thoracic incision But often it is necessary to incise the pleura and occasionally better exposure is obtained by an incision to the right of the sternum Positive pressure anesthesia with endotracheal intubation is necessary in the presence of extensive lacerations of the pleura Ligation of the internal mammary or of an intercostal or coronary artery may be required for the control of bleeding Bleeding from the heart or from a coronary artery is usually associated with an intrapericardial clot which should be evacuated The surgical technique has been described by Maynard et al [70]

If the outstanding clinical signs are those of cardiac compression oxygen is administered a dextran or plasma infusion or blood transfusion is started and the pericardium should be promptly aspirated preferably by the costoxiphoid or left fourth or fifth intercostal approach Recovery may follow paracentesis even when there is massive hemopericardium [66] If tamponade recurs following temporary relief, aspiration should be repeated However, operative intervention is indicated if the signs of compression are not relieved or recur promptly or repeatedly Although recovery has been reported following non operative treatment,[60] [18] cardiac tamponade should not be allowed to persist for many hours because of the danger of the irreversible changes of shock such as renal insufficiency [11] When hemothorax accompanies hemopericardium, early and repeated aspiration of the pleural cavity without air replacement is necessary to permit undelayed expansion of the lung and to avoid hemofibrothorax

If a *foreign body in the heart* is presented soon after the accident prompt removal may be advisable in order to avoid the danger of cardiac erosion, hemorrhage rupture or infection (bacterial endocarditis or myocardial abscess), recurrent pericardial effusion injury to a coronary artery, and the possibility of embolic vascular occlusion [11] Operation may be indicated to prevent or cure a psychoneurosis due to the patient's knowledge that there is a foreign body in his heart In general, very large foreign bodies those with sharp edges or points, those which are free in a cardiac chamber and those which impinge on the valve or myocardium during systole should be removed [31] In the absence of symptoms the foreign body may be left in situ if continued observation discloses no change in its position If the foreign body is discovered accidentally weeks months or longer after the injury it is undesirable to attempt removal if there is evidence that the object is fixed by scar tissue But an exploratory operation may be necessary if the patient has complaints which appear to be referable to the foreign body e g, pain or a cardiac neurosis develops because of the presence of pain Many instances have been reported of the successful removal of foreign bodies including bullets shell fragments and needles [35] Harken[35] reported no deaths in a series of 131 patients operated for foreign body in the heart or great vessels

The results of surgical operations for penetrating wounds of the heart have been reported by Bigger,[12] Elkin [7] and others [67] [35] [70] Bigger[12] estimated the mortality of cardiac suture to be about 30 per cent Elkin [7] obtained recoveries in 22 of 38 patients on

whom he operated for cardiac wounds. The mortality in the series of operated cases reported by Griswold and Drye[37] decreased from 46 per cent between 1933 and 1934 to 31 per cent *with an operative mortality of 25* per cent in subsequent years. Complete recovery may follow even when a major coronary artery must be ligated.[38] Cardiac infarction need not follow. Follow up studies of 119 cases of cardiac wounds in which the patient survived operation disclosed restoration of function that was complete in 77.3 per cent, fair in 22.7 per cent and poor in 1.7 per cent.[44] Ligation of the anterior descending branch of the left coronary artery did not influence the result. The site of the sutured wound heals to a firm scar. A series of such cases in which the heart was later studied histologically has been collected and reported by Gronwald.[43] In a series of 28 cases of penetrating wounds of the heart treated by non *operative means (cardiac aspiration and* transfusion) the mortality was only 10.7 per cent.[20]

NON PENETRATING INJURIES OF THE HEART

Increasing recognition has been given in recent years to the occurrence of cardiac damage following a non penetrating blow to the chest wall. Our knowledge of these non penetrating cardiac lesions has been especially enhanced by the studies and reviews of Barger,[4] Beck,[9] Warburg[9, 34] and others. The following discussion is designed to call attention to the occurrence of cardiac damage from blunt injury to the chest wall but at the same time to caution against attributing to a preceding trauma a host of unrelated cardiac disturbances which are the consequences of the natural course of underlying independent organic heart disease.

Contusion or rupture of the heart following a blow to the chest was demonstrated experimentally in rabbits and dogs by Kulbs,[69] Schlomka[88] and by Kissane, Fidler and Koons.[85] By controlled measured forces which struck but did not penetrate the chest wall they were able to cause subepicardial and subendocardial myocardial hemorrhages and hemopericardium, cardiac necrosis and heart failure, arrhythmias and various electrocardiographic abnormalities and sudden death due to ventricular fibrillation or cardiac standstill. More severe injuries including cardiac rupture and lesions resembling myocardial infarction were noted when the blows were applied directly to the exposed hearts of animals.[74]

Support for the concept of cardiac disease following blunt injuries of the chest wall is also provided by numerous clinical and pathologic observations.[34, 49, 83, 8, 4, 85] Necropsy studies had long ago demonstrated that fatal rupture of the heart can follow a severe blunt injury to the chest.[34] Recently, rupture of the heart following a non penetrating injury was diagnosed during life and the ruptured myocardium was successfully sutured.[4] But only recently has emphasis been placed on the frequency of less severe cardiac injuries with asymptomatic recovery or of survival with a variety of transient or persistent and serious cardiac symptoms. In an analysis of 175 cases of non penetrating wounds of the heart Bright and Beck[16] found 152 instances (87 per cent) *of death from cardiac rupture (proven by* necropsy), 11 instances (6 per cent) of death from myocardial failure and only 12 instances (7 per cent) of recovery. Beck[9] believed that the percentage of recoveries was much higher but that there was a failure to recognize or a fear to diagnose clinical heart disease due to cardiac contusion.

In some cases the demonstration of hemopericardium by paracentesis following non penetrating chest trauma strongly supports the clinical diagnosis of cardiac contusion. More often in reported cases in which transient or persistent clinical manifestations are interpreted as evidence of myocardial damage or of acute or chronic heart failure due to cardiac contusion there is great uncertainty as the the accuracy of the diagnosis or interpretation. In particular it seems to me that neurocirculatory asthenia or cardiac neurosis, independent coincident cardiovascular disease, reflex cardiovascular disturbances following trauma and its emotional concomitants and pulmonary embolism have been interpreted in different cases as heart disease due to cardiac contusion.

ETIOLOGY

Direct Non penetrating Blunt Injury

A frequent cause of non penetrating cardiac injury is the well publicized steering wheel accident.[27, 9] The driver's chest is pinned against the steering wheel when the forward momentum of the car is suddenly arrested

Severe cardiac injury or rupture of the heart often follows crushing chest accidents when an auto train or other vehicle runs over the prostrate body Falls from a great height result in similar cardiac damage often associated with serious injuries in other parts of the body Direct blows to the anterior chest wall by a baseball golf or tennis ball traveling at high speed, by heavy falling or swinging objects which strike at great velocity fist blows, kicks by a horse or other powerful animal and compression of the chest between two moving objects are among other causes of non penetrating cardiac trauma In battle experience blast injuries form an additional causative mechanism

As a rule the non penetrating force strikes over the precordium but cardiac injury occasionally follows blows to the posterior thorax abdomen or lumbar region Serious contusion and even rupture of the heart often occurs without any significant visible external injury of the chest wall and without fracture of the ribs[16, 9, 8] In fact in the series of 250 non penetrating chest injuries reported by Arenberg[2] the greater cardiac damage occurred among the cases without rib fracture Conversely bilateral multiple fractured ribs were usually unaccompanied by cardiac damage And among the 152 cases of ruptured heart following non penetrating injuries of the chest assembled by Bright and Beck[16] evidence of fractured ribs was found only in 58

Clinical and experimental observations suggest that blunt injury is more likely to damage the diseased heart than the normal one Kulbs and Strauss[61] found that the hearts of rabbits previously rendered atherosclerotic and the hearts of dogs intoxicated with excessive doses of digitalis or thyroxin were more readily injured by blunt force applied to the chest than were the normal hearts of these animals It may be that diseased human hearts are similarly more susceptible to non penetrating blows, but preexisting cardiac disease is by no means as important a predisposing factor as in the cases of cardiac injury following unusual and severe physical strain

Cardiac Strain

In discussions of non penetrating cardiac trauma there is often a lack of distinction between lesions produced by blunt injuries to the chest wall and those due to overstrain of the heart Cardiac strain refers to the anatomic lesions and functional disturbances which result from some intense and unusual physical effort Because this type of traumatic heart disease is frequently involved in compensation and other medicolegal problems and because it rests on less scientific foundation than the type due to blunt injury of the chest wall, it should be distinctly segregated

There is always uncertainty about reported instances of damage to the normal heart due to physical effort Doubt usually surrounds the claim that the heart was previously normal When arrhythmias follow a physical strain there is also a question of coincidence, for arrhythmias not infrequently arise in the normal heart without unusual effort or other apparent cause

The so called "athlete s heart,' i e cardiac dilatation and hypertrophy formerly attributed to athletic activity, is now believed to be the consequence of independent rheumatic congenital or syphilitic heart disease Transient cardiac enlargement occurs occasionally during strenuous physical exertion but this is a reversible compensatory dilatation (p 94) which disappears promptly with cessation of the activity[25, 84] There are no well authenticated cases of congestive heart failure developing as a result of a physical effort in an individual with a normal heart Disorders of rhythm, including premature beats paroxysmal tachycardia and even atrial fibrillation may first appear in a normal heart after strenuous exertion much more commonly this sequence is observed when there is underlying cardiac disease Rarely is a normal valve or chorda tendinea ruptured by physical exertion Physical effort especially in combination with emotional stress commonly induces a paroxysm of angina pectoris but only in subjects with advanced coronary atherosclerosis or other disease diminishing the coronary reserve The precordial oppression sometimes experienced by normal subjects during a prolonged race and before ' second wind may represent angina pectoris due to functional coronary insufficiency but this disappears rapidly and recurs only with very unusual and strenuous exertion

In the previously diseased heart the strain of physical effort apparently may induce the disorders of rhythm already mentioned rupture of a valve chorda or papillary muscle, a paroxysm of angina pectoris and occasionally congestive heart failure Severe

prolonged exertion is theoretically capable of causing myocardial necrosis without coronary occlusion but there is great controversy as to whether it ever precipitates the occlusion itself (p 494) Physical effort in contrast with blunt injury to the chest wall is not the cause of pericarditis myocardial contusion or rupture The specific cardiac lesions attributed to non penetrating injuries and to cardiac strain are discussed under Pathology

PATHOLOGY OF NON PENETRATING CARDIAC TRAUMA

The pericardium and myocardium are most frequently injured by blunt injuries of the chest the valves or their attachments are most commonly said to be torn by an unusual physical effort

The Pericardium

Fibrinous pericarditis and hemopericardium result from non penetrating trauma the latter much less frequently than after penetrating wounds Contusion of the pericardium and epicardium is probably fairly common but is easily overlooked in non fatal cases because of the paucity or absence of physical signs and symptoms Pneumopericardium and hydropericardium have been reported [67] Occasionally a non penetrating cardiac trauma stirs up a tuberculous or purulent pericarditis

The Myocardium

The myocardium may be merely bruised (cardiac contusion) it may be partially lacerated or it may suffer a through and through perforation involving the wall of one or more chambers or of the septa (rupture of the heart) [6] Traumatic rupture of the heart may occur with an intact pericardium [15] Bright and Beck[18] assembled 152 cases of rupture of the heart in which the various chambers were involved with almost equal frequency but in which the left ventricle and right atrium predominated In addition in this series the interventricular septum was perforated 13 times the interatrial septum once and multiple chambers 13 times Isolated traumatic rupture of the interventricular septum following blunt force has been reported in a previously healthy 21 year old man [73] The papillary muscle may be ruptured by blunt injury to the chest as in the cases reported by Kleberger[67] and by Glendy and White [34] *Rupture of the heart may occur promptly* after the injury but there is often an interval *of five to fifteen days before the hemorrhagic disorganized softened area perforates* [76 95]

Rupture of the heart is a fatal consequence of the most intense crushing injuries of the chest wall Of greater clinical interest and importance are the less severe contusions characterized by less extensive subendocardial and subpericardial myocardial hemorrhage and dissolution of tissue often associated with overlying local pericarditis As in the experimentally induced cardiac contusions [74] these bruised areas of heart muscle *may heal with the formation of a firm scar in*distinguishable from the scar of a cardiac infarct due to coronary artery occlusion [44] That cardiac contusion may be followed by cardiac aneurysm is suggested by the report of Joachim and Mays [64] Endocardial thrombosis and cerebral embolism may also follow contusion of the heart [77]

Coronary Thrombosis and Myocardial Infarction

The effect of non penetrating chest injuries and of physical strain must be considered The above mentioned form of myocardial hemorrhage necrosis and scarring caused by a blunt chest injury (contusio cordis or commotio cordis) should be distinguished from the cases of myocardial infarction secondary to atherosclerotic coronary occlusion in which the coronary occlusion is believed to have been precipitated or accelerated by the strain of some physical exertion [73 80] The possible causal relationship of atherosclerotic coronary occlusion to physical strain has come to assume medicolegal importance particularly in connection with insurance and workmen s compensation This problem has been discussed under the heading of etiology of acute coronary occlusion (p 494)

In many reported cases the sequence of events after a severe and unusual physical strain strongly suggests that the strain in some way initiated or accelerated the coronary artery occlusion and the consequent infarct [73 84] There is no doubt that the fundamental cause of the occlusion in these cases is atherosclerosis but the unusual effort is believed to precipitate the occlusion either by causing intimal hemorrhage in the atherosclerotic plaque or by some other undetermined mechanism Master[83] and his associates have marshalled considerable evidence to

refute these interpretations but admit that in 2 per cent of a large series of cases of coronary artery occlusion there was a chronologic if not causal relation to unusual exertion Since about 500 000 cases of coronary occlusion occur annually, *at least the possibility that* effort is a precipitating factor must be considered in 10 000 cases Certainly this relationship should be given credibility in relatively few instances of this potential group

Occasionally a strenuous or unusual exertion occurs in a person with severely narrowed (atherosclerotic) coronary arteries The exertion may so intensify the coronary insufficiency relative to the needs of the myocardium that myocardial anoxia and necrosis develop usually in the subendocardium of the left ventricle and papillary muscles Such cardiac necrosis without recent coronary occlusion[10] may present a clinical picture identical with that of acute coronary thrombosis, there may be symptoms of angina pectoris with corresponding electrocardiographic changes or there may be no detectable clinical manifestations

Finally there are instances in which a blunt injury to the chest wall did not cause a cardiac contusion but purportedly precipitated a coronary artery occlusion and myocardial infarction [95, 63, 82] Injury to the heart may possibly cause a thrombosis of a coronary artery[34] or, as a better established fact a necrosis of cardiac muscle simulating infarction without coronary thrombosis Or a coincidental atherosclerotic coronary thrombosis may follow a non penetrating blow to the chest and be attributed to that trauma *Great care is necessary in interpretation* Thus in the case reported by Kienle[63] of a 40 year old man who fell while skiing and then experienced the typical clinical course of coronary occlusion and posterior wall infarction one must consider not only the possibility of coincidence but also the possibility that the occlusion was the cause not the consequence of the fall In some instances the youth of the patient is used to support the interpretation that the blunt chest injury and not the natural course of preexisting disease was responsible for the coronary occlusion The report of MacDonald[65] concerns a 21 year old man who was struck on the chest by a soft ball There was clinical and electrocardiographic evidence of myocardial infarction Postmortem examination disclosed old and recent coronary occlusions However, recent studies have amply demonstrated that the premature occurrence of advanced coronary atherosclerosis is no rarity [29] In clinical reports without autopsy studies it is always *difficult to differentiate* between cardiac contusion following blunt chest injuries and coincident or causally related coronary artery occlusion

Valvular Lesions

Rupture of a valve or of chordae tendineae may follow non penetrating injury to the chest or severe physical strain More often the affected valve is the seat of preexisting rheumatic, syphilitic, congenital or atherosclerotic disease but normal valves have also been lacerated or perforated by these forms of indirect trauma

In experimental cardiac contusions in animals valvular hemorrhages were sometimes seen but no ruptures [59] Barié[5] found in his experiments with human hearts *post mortem* that extremely high pressures were required to rupture a valve Nevertheless there are apparently well authenticated cases of rupture of normal human valves as a result of both physical exertion and non penetrating injury to the chest Fourteen such cases were assembled from the literature by Adam[1] who also reported a case of his own Howard[44] reported an instance of traumatic aortic insufficiency due to rupture by strain of a normal aortic valve, while Kissane, Koons and Fidler[48] described a proven case of rupture of the aortic valve due to crushing injury to the chest following an explosion Proudfit and McCormack[79] described a case of aortic insufficiency *due to rupture* of the aortic valve following an automobile accident in which there was good therapeutic control of the initial symptoms during the terminal 14 months of life Diagnosis of a ruptured aortic valve is important because of the possibility of surgical correction of the resulting aortic insufficiency [41]

The aortic valve is most commonly affected[18, 84], the mitral valve is next in frequency of involvement while the pulmonic and tricuspid valves are torn more rarely The greater frequency of the left sided valvular injuries may be attributed both to the higher intracardiac pressures on that side and to the greater frequency with which these valves are the site of underlying disease Injuries to the mitral valve include tears of the cusp itself or

more commonly rupture of chordae tendineae or occasionally of a papillary muscle Rupture of apparently normal mitral chordae following severe exertion was reported by Frothingham and Haas[31] Rupture of the mitral chordae may occur spontaneously usually as a result of underlying bacterial endocarditis Bailey and Hickam[3] reported 7 cases of spontaneous rupture of mitral chordae tendineae in which rheumatic endocarditis was the underlying condition In such cases of spontaneous rupture of diseased valves the actual event may be attributed properly or improperly to some physical effort In the cases reported by Bailey and Hickam[3] the histories failed to indicate that vigorous exertion or external trauma was of primary importance in the rupture

Other Cardiac Lesions Attributed to Indirect Trauma

Acute and subacute bacterial endocarditis suppurative myocarditis and pericarditis have each at times been ascribed to commotio cordis In these cases the injury is credited with creating a locus minoris resistentiae lighting up a latent infection or permitting the entrance of bacterial agents which then produce bacterial endocarditis in a heart predisposed by an underlying valvular lesion[33] However in some of the recorded cases the clinical diagnosis of endocarditis is questionable and in all the cases of subacute bacterial endocarditis the insidious onset of the disease makes it impossible to relate it accurately in point of time to the trauma Sometimes traumatic lesions in distant parts of the body or in the lungs pleura or mediastinum lead to infections which later extend to the pericardium or heart

CLINICAL FEATURES OF NON PENETRATING CARDIAC TRAUMA

Rupture of the heart is rapidly fatal but occasionally not until the second week after the injury On the other hand mild cardiac contusion may be asymptomatic When symptoms do develop they may appear immediately or after a variable interval of days or even weeks There may or may not be a loss of consciousness even after serious blows to the chest wall

Chest pain is probably the commonest complaint after nonpenetrating trauma but its onset may be delayed for several hours This may arise in the traumatized chest wall the pleura pericardium or the heart A persistent or recurrent dull ache in the precordium or apical region may be a symptom of cardiac neurosis following trauma Occasionally a severe or unusual exertion or a non penetrating chest injury precipitates the first attack of typical angina pectoris[55] The angina pectoris may be due exclusively to cardiac contusion but as a rule there is underlying atherosclerotic coronary artery disease or syphilitic coronary ostial narrowing[54] Prolonged cardiac pain with all the other features of acute coronary thrombosis has been recorded following cardiac contusion[11]

Weakness is a frequent complaint after cardiac contusion or after valvular rupture It usually subsides after a brief period but may persist especially if cardiac failure develops

Palpitation may result from tachycardia arrhythmia or exaggerated awareness of the normal heart beat

Disorders of rhythm and rate are among the commonest reported manifestations of non penetrating cardiac trauma *Tachycardia* is common but sinus bradycardia has also been recorded[40] Usually the tachycardia is transient but may persist in the presence of cardiac neurosis Occasionally ventricular tachycardia and ventricular fibrillation have been noted *Atrial fibrillation* usually transient is the commonest important arrhythmia associated with non penetrating cardiac trauma or severe effort[4] It may occur in the previously healthy heart[49 4] In Warburg s[61] series there were at least 32 instances of atrial fibrillation or about one third of the entire group In nearly half of the cases the arrhythmia persisted *Atrial flutter* has also been recorded[31] *Heart block* incomplete[33] or complete[11] has been observed on occasion This may be due to traumatic hemorrhage into the conduction tissues But unless the subject has been examined previously congenital heart block is difficult to exclude (p 389) Transient *right bundle branch block* was recorded in a young man of 22 following a blow on the chest when thrown from his motorcycle[41] Transient disturbances in conduction following non penetrating trauma in 3 cases were reported by Taylor[9]

Congestive heart failure commonly follows severe injuries to the heart It may start rapidly after the trauma with progressive acute pulmonary edema or it may evolve more slowly from symptoms of mild left heart

failure to advanced left- and right sided con gestive heart failure But in cases of rupture of a valve or its chordae, signs and symptoms of heart failure may not appear for many months Heart failure may also result from prolonged paroxysmal tachycardia or atrial flutter or fibrillation and rapid ventricular rate When there are only a few symptoms such as dyspnea and fatigability, the diagnosis of heart failure should be differentiated from cardiac neurosis and pulmonary injuries

Enlargement of the heart is usual in those individuals who develop heart failure after cardiac trauma But hemopericardium may simulate cardiac enlargement and by causing cardiac tamponade may produce symptoms of congestive heart failure

Angina pectoris and manifestations of cardiac infarction have been mentioned *Sudden death* may occur after cardiac trauma with or without preceding symptoms of angina pectoris

Distinctive clinical features may be produced by *rupture of valves* or by *pericarditis and hemopericardium* Rupture of a valve or chorda tendinea may be characterized by sudden onset of precordial pain, dizziness weakness breathlessness palpitation or shock The diagnostic feature is a very loud coarse precordial murmur In aortic lesions, there is an aortic diastolic murmur with the usual circulatory dynamics accompanying aortic insufficiency The diastolic murmur of aortic insufficiency due to rupture of the aortic valve may have a distinctive musical quality described as sea gull spinning top or cooing dove, but this is not heard in all cases The sea gull type of murmur is heard more commonly in aortic insufficiency due to destruction of the aortic valve in bacterial endocarditis and in syphilitic aortic insufficiency with eversion of the right anterior aortic cusp (p 688) In cases of rupture of the mitral valve or chordae there is a loud systolic murmur maximal at the apex and left sternal border, usually accompanied by a thrill and occasionally accompanied by an apical diastolic murmur Cardiac enlargement and congestive heart failure usually develop gradually after many months Rupture of a papillary muscle may give similar signs, but there is likely to be a rapid development of acute left heart failure and death within hours or days Recent previous cardiac examination with negative findings is an important and often the decisive clue to diagnosis

Superficial *pericarditis* may be disclosed by the presence of a friction rub or there may be associated physical, roentgenologic and electrocardiographic signs of pericardial effusion With rupture of the heart there is likely to be a hemopericardium which causes cardiac tamponade[11] Extensive hemothorax is commonly associated due to rupture into the pleural cavity

Electrocardiographic changes may result from pericarditis or hemopericardium, from direct myocardial injury or from myocardial necrosis secondary to thrombosis of a coronary artery In cases of pericarditis caused by non penetrating chest injuries, Wood[38] described electrocardiographic abnormalities similar to, though often distinguishable from those characterizing myocardial infarction He emphasized that in cases of cardiac contusion T wave inversion and ST deviations were most striking in lead II while in cardiac infarction discordant ST and T wave changes were most apparent in leads I and III Burstein and Marshak[17] reported two cases of cardiac contusion with electrocardiographic findings of T wave depression or inversions in one of which these abnormalities alone permitted the diagnosis The precordial lead disclosed the earliest and most constant findings

Numerous reports of cardiac injury by penetrating or non penetrating trauma have confirmed the occurrence of ST elevations or depressions or T wave inversions but no uniform pattern has been described Apparently the site and extent of the lesion and the interval between the injury and electrocardiographic examination account for the described variations As a rule ST and T wave changes are transient and disappear within a few weeks and almost always within three months In addition to the above the electrocardiograph may disclose transient or persistent atrial fibrillation, heart block or bundle branch block

DIAGNOSIS

The diagnosis of cardiac contusion must be entertained whenever an individual experiences a blunt injury of the chest wall In general the greater the momentum of the blow and the greater the proximity to the precordium, the more likely the cardiac injury Occasionally cardiac contusion or rup-

ture follows extreme compression of the abdomen or thighs[3]

Serial electrocardiograms should be taken in all cases of chest trauma Depressed or inverted T waves atrial fibrillation or heart block may suggest cardiac injury whether clinical symptoms and signs are present or not Roentgenologic films of the chest should be made to study the size form and pulsations of the cardiac silhouette Such study may determine the presence of pericardial effusion and serves also to exclude pulmonary lesions as the possible cause of the patient s symptoms

Pericardial paracentesis should be performed if there are physical or roentgenologic signs of pericardial effusion or if there are symptoms and signs of acute cardiac tamponade If there are symptoms and signs of acute circulatory failure the findings should be reviewed to determine the presence of cardiac compression Hemopericardium following a non penetrating chest injury suggests cardiac contusion and perforation of a chamber or laceration of a coronary artery

The diagnosis of cardiac damage to non penetrating trauma should also be considered if a pericardial friction rub appears soon after the injury if loud murmurs or thrills develop or if clinical or electrocardiographic signs of cardiac anoxia or cardiac infarction appear

The presence or absence of preexisting disease is often of primary importance in the interpretation of post-traumatic symptoms and signs Since cardiac trauma is often likely to involve insurance workmen s compensation or liability problems careful cardiac examination when insurance is first granted and when the patient is first seen after an accident are essential

PROGNOSIS

There are inadequate data for definitive statements as to prognosis Rapid fatalities follow rupture of the heart either immediately after the injury or a week or two later Less serious but severe injury may be complicated by heart failure angina pectoris or evidence of myocardial infarction The outlook is then similar to that in cases due to non traumatic causes Rupture of a valve is usually followed by fatal heart failure within a year or two Arrhythmias such as paroxysmal tachycardia atrial fibrillation and heart block usually disappear within a few days or weeks but may be prolonged and may be complicated by heart failure Greater recognition of the frequency of cardiac contusion and more careful diagnostic methods are leading to discovery of the mild cases in which recovery is the rule[2]

TREATMENT

In cases with very severe injuries and rupture of the heart death often occurs too rapidly to permit surgical treatment But when a sufficient interval elapses and there are signs of increasing cardiac compression pericardial aspiration should be performed If hemopericardium is proved and no relief is obtained or if following aspiration there is only transient improvement with recurrent relapse surgical exploration of the heart should be undertaken If a cardiac rupture is discovered it should be sutured as noted above (p 1060) or a pericardial graft can be sutured over a softened area The use of the newer blood products and absorbable gelatin or cellulose preparations[47] may be valuable to control bleeding of softened areas as in rupture of the liver In cases of ruptured aortic valve an artificial aortic valve may be inserted into the descending aorta[31] (p 692)

In patients with symptoms such as weakness arrhythmia angina pectoris or heart failure or in patients with significant electrocardiographic changes sharp restriction of activity or limited confinement to bed for three to six weeks or longer may be necessary to avoid rupture of a lacerated myocardium The usual measures designed to control heart failure cardiac pain or cardiac arrhythmias should also be instituted

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Chapter 45

CARDIAC TUMORS

Tumors of the heart and pericardium have evoked an extensive literature out of all proportion to their uncommon incidence and their relative unimportance as a cause of clinical heart disease This unusual interest has been aroused by four aspects of the subject

(1) Uncertainty as to the nature and pathogenesis of cardiac myxoma and rhabdomyoma

(2) The occurrence of clinical features which may simulate those of common forms of heart disease

(3) The ability to diagnose cardiac tumors during life

(4) The possibility of surgical removal and cure of certain cardiac tumors

INCIDENCE

There have been many reviews of the literature on cardiac neoplasms [60, 111, 59, 85, [illegible], 28, 31, 38] Lymburner[55] encountered only 4 primary tumors of the heart (0 05 per cent) and 52 secondary tumors (0 6 per cent) in a series of 8500 autopsies at the Mayo Clinic Similarly Pollia and Gogol[71] discovered only 29 secondary tumors (0 25 per cent) in 12,000 autopsies and Scott and Garvin[88] 118 metastatic neoplasms of the heart and pericardium (1 0 per cent) in a series of 11 100 postmortem examinations Malignant neoplasms of the heart and pericardium compose [illegible] to 11 per cent of malignant tumors of all kinds throughout the body [106, 85, [illegible]] According to Prichard,[73] a metastatic cardiac neoplasm was discovered at autopsy in 326 (3 9 per cent) of 8414 cases in which death was due to cancer A higher incidence was reported by Young and Goldman [112] and by Bisel et al [illegible] (21 per cent of 500 cases of neoplastic disease)

CLASSIFICATION

Cardiac tumors may be classified as follows

(I) Primary tumors of the heart
- (A) Benign
  - (1) Myxoma
  - (2) Rhabdomyoma
  - (3) Other rarer tumors
    - Fibroma lipoma angioma papilloma teratoma leiomyoma xanthoma
- (B) Malignant
  - (1) Sarcoma—various types
  - (2) Other rarer malignant tumors
    - Mesothelioma or mesothelial sarcoma of the pericardium rhabdomyosarcoma epicardial epitheliomas

(II) Secondary (malignant) tumors
- (A) Carcinoma and occasional sarcoma by direct invasion
- (B) Carcinoma or sarcoma by metastasis
- (C) Systemic neoplastic disease with cardiac involvement
  - (1) Hodgkin s disease
  - (2) Lymphosarcoma
  - (3) Leukemia
  - (4) Kaposi s sarcoma
  - (5) Neurofibromatosis (von Recklinghausen s disease)

PATHOLOGY

PRIMARY TUMORS

Lymburner[44] was able to collect 226 instances of primary cardiac tumors from the literature in 1934 but by 1951 Prichard[73] found 415 such reported cases Approximately three fourths of the primary tumors were benign Myxoma, sarcoma and rhabdomyoma are the commonest primary tumors in the given order of frequency The myxoma the polypoid fibroma and sarcoma arise from the endocardium Rhabdomyoma and fibroma arise from the myocardium while mesothelioma or mesothelial sarcoma lipoma fibroma angioma are among the tumors of pericardial origin

Benign Primary Tumors

Myxoma The myxoma is a solitary globular or polypoid tumor varying in size from that of a cherry to a large peach It is semi translucent, yellowish gray in appearance and elastic and gelatinous in consistency Its cut surface is mucinous or gelatinous and may be more or less hemorrhagic The myxoma occurs chiefly in the left atrium arising usually from the atrial septum near the rim of the fossa ovalis to which it is attached by a short stalk From this pedicle the myxoma extends to fill some or most of the atrial cavity and may even occlude the mitral orifice and produce all the disturbances of a mitral stenosis including right ventricular hypertrophy and pulmonary vascular changes The myxoma may be the source of coronary and cerebral embolism [11] The myxoma may also arise near the margin of the left atrial appendage or less often from the right atrium or ventricles A myxoma of the left ventricle with occlusion of the abdominal aorta and renal arteries by tumor embolus was reported by Young and Hunter [113] In another case myxomatous embolic occlusion of the abdominal aorta was responsible for the earliest clinical symptoms [illegible]

Microscopically the myxoma is seen to be composed of an amorphous or mucoid matrix with characteristic stellate or spindle shaped cells acini of large polyhedral cells, delicate scanty blood vessels, occasional lymphocytes and plasma cells small hemorrhages or blood pigments (hemosiderin or hematoidin) and very small amounts of collagenous and elastic fibers Variations in the appearance and predominance of these individual microscopic elements of myxoma account for other names applied to this tumor, e g hemangio or fibro-myxoelastoma,[14] lymphangioendothelioma [66] fibromyxoma, fibroma, hemangio myxoma

The weight of evidence appears to favor the concept that the myxoma is a true neoplasm,[111, illegible] as maintained by Ribbert [78] The neoplasm may arise in rests of embryonic mucoid tissue or it may represent an endothelioma with myxomatous degeneration [66] However, following the interpretation of Thorel,[101] many writers view the myxoma as a thrombus which has swollen by imbibition and undergone organization [illegible] In the case reported by Dexter and Work [27] the authors suggested that rheumatic inflammation of the left atrium predisposed to the formation of the myxoma, but rheumatic lesions have not been reported in other cases of myxoma

Myxomata of the cardiac valves have been described as distinctive shaggy tumor masses which are probably true tumors but have also been interpreted as exaggerated Lamblian excrescences Fibroma of the valves has been described [95] This occurs as a solitary round or oval, broad or pedunculated solid tumor with a slight predilection for the tricuspid valve It is probably a true tumor arising from the valvular subendothelium but it has also been interpreted as an organized thrombus

Rhabdomyoma The rhabdomyoma is a congenital glycogen-containing tumor which occurs as multiple or solitary nodules or as a diffuse infiltration of the myocardium [30, 4] There is a difference of opinion as to whether the tumors actually contain glycogen Most frequently there are multiple gray or purplish nodules lying within the myocardium bulging externally on the epicardial surface, or projecting into the lumen of the cardiac chambers They occur oftenest in the left ventricle but may affect any portion of the heart including the valvular leaflets Less often there are solitary nodules which are usually located in the region of the apex Solitary tumors on the valve may produce murmurs or a tumor of the conduction system may cause heart block or an arrhythmia Occasionally there is diffuse cardiac involvement and enlargement without distinctive tumor formation, this type of case may be a form of glycogen storage disease [60] Sudden death, or death within a few hours after onset of dyspnea and cyanosis, may occur

According to Batchelor and Maun [4] 63 authentic cases of rhabdomyoma had been described since the first case reported by von Recklinghausen[74] in 1862 In most instances death occurs in the first year of life and in 85 per cent before puberty A striking feature is the usual association of multiple cardiac rhabdomyoma with tuberous sclerosis of the brain, multiple tumors of the kidney and adenoma sebaceum of the skin [4] The solitary cardiac rhabdomyoma is not accompanied by such lesions This combination of tumor like deformities in several organs simultaneously has cast doubt on the concept of Wolbach[109] and others that rhabdomyoma is a true tumor of embryonal cardiac muscle cells Instead the teratogenetic character of the tumorlike

lesions suggests that they represent simultaneous tissue malformations in the various organs The term hamartoma[2] has been applied to these tumor like formations caused by errors in tissue development[34] Occasionally fibrosis and calcification occur in a rhabdomyoma features which have led Olsen and Cooper[6] to interpret the nodules as resulting from congenital glycogenic degeneration of the myocardium

Microscopic examination of cardiac rhabdomyoma discloses a spongy tissue containing many large stellate cells which form peculiar vacuolated structures These vacuoles lie within the cell body of large embryonic like muscle fibers[48] and have been said to contain glycogen as may be demonstrated by Best s carmine stain[1]

Other benign primary tumors have been described in solitary case reports *Fibroma* of the valves has been mentioned Fibroma may also occur as a solid gray or white polypoid tumor of the left or right atrium or as a more or less circumscribed mass within the myocardium of the ventricles or ventricular septum *Lipoma or fibrolipoma* occur occasionally as a single tumor of great size or in the form of multiple fatty tumors Cases of lymph angioendothelioma reported by Armstrong and Monckeberg[1] and by Lloyd[58] are of special interest because they involved the atrioventricular node and caused heart block Teratoma arising in the mediastinum may rarely involve the pericardium[48, 107] and cause symptoms of acute or chronic cardiac compression or may become infected and produce symptoms of purulent pericarditis[6]

Malignant Primary Tumors

Primary Sarcoma Sarcoma of the heart is the almost exclusive representative of primary malignancy of this organ Many varieties have been described including fibrosarcoma spindle cell sarcoma round cell giant cell myxosarcoma rhabdomyosarcoma[54, 9] and mesothelioma (mesothelial sarcoma endothelial sarcoma) Kaposi s sarcoma of the heart[105] has sometimes been reported under the heading of angiosarcoma[104] angioendothelioma[41] and angioreticuloendothelioma[19] The sarcoma may arise from the endocardium or pericardium or more rarely from the myocardial layer (rhabdomyosarcoma)

According to Prichard[73] 113 cases of primary sarcoma of the heart and pericardium had been reported by 1951 In about 50 per cent of the cases in which the site was mentioned the malignant tumor arose from the right atrium[104] This contrasts with the commonest benign tumor (myxoma) which arises usually from the left atrium Primary sarcoma may also originate in the pericardium[93] but only 22 cases had been reported up to 1947[75] Isolated instances of sarcoma of the left atrium[47] or other portions of the heart have also been noted Mahaim[59] has described cases of mesothelioma arising from epicardial inclusions in the septum near the a v node

The primary cardiac sarcoma metastasizes most commonly to the pleura and lung but also to the mediastinal tracheobronchial or retroperitoneal lymph nodes to the adrenals to other parts of the heart or to the brain Haythorn et al[45] described a case of primary fibromyxosarcoma of the heart and pulmonary artery with extensive metastasis along the pulmonary arterial tree bronchi and lungs The roentgenologic appearance resembled that of carcinoma or Hodgkin s disease of the lungs

The primary sarcoma arising from the right atrium is usually a large firm gray or yellowish papillary tumor which may fill most of the atrial cavity it may extend toward the right ventricle to occlude the tricuspid orifice or it may invade or occlude the venae cavae

Pericardial sarcoma forms a more diffuse white or yellowish tumor mass often of massive thickness (1 to 5 cm) and extent which deforms or obliterates the cardiac contours and partially or completely glues the pericardial layers[93, 67] The tumor itself reveals many areas of hemorrhage and necrosis It may be confined entirely to the pericardium it may compress the myocardium from without or it may actually invade the heart muscle and replace more or less extensive portions The base of the pulmonary artery and aorta may be incorporated in the dense tumor mass and rendered relatively fixed The pericardial cavity often contains a serofibrinous or serohemorrhagic effusion which occasionally becomes infected Pleural effusions sometimes bloody may be associated either due to direct neoplastic invasion of the pleura or secondary to cardiac compression and heart failure

SECONDARY (METASTATIC) CARDIAC NEOPLASMS

Secondary tumors occur with much greater frequency than primary tumors of the

heart[73, illegible, illegible, 39] In a recent series of 2547 consecutive cases studied at necropsy at the Walter Reed Army hospital including 980 cases of malignant disease the incidence of metastatic neoplasms of the heart was 5 3 per cent of the entire series and 13 9 per cent of the malignant cases[25] Cohen and associates[21] encountered 65 tumors metastatic to the heart or pericardium among 315 malignant tumors, an incidence of 20 6 per cent Most of the secondary tumors are carcinomata but metastatic sarcomata also occur Carcinoma usually appears as single or multiple discrete small white firm nodules but it may occur as a more diffuse infiltration and occasionally as a single metastasis Carcinoma of the heart may also present as miliary infarction without gross metastases Carcinomatous emboli may be observed in branches of the coronary arteries A carcinomatous lymphangitis may occur Sarcoma occurs chiefly as diffuse infiltrating masses in the pericardium and myocardium They may broaden the cardiac walls and may encroach on the cardiac cavities or protrude externally Like primary sarcoma secondary sarcoma of the pericardium may produce massive thickening of the pericardium a serofibrinous or fibrinopurulent effusion which is often hemorrhagic, or a completely adherent pericardium Malignant melanoma and leukemia are particularly likely to spread to the heart or pericardium [illegible] Bisel et al[10] found the over all incidence of cardiac infiltration in 119 patients with leukemia to be 44 per cent

Metastatic neoplasms may invade any part of the heart including the pericardium the ventricles atria ventricular septum and occasionally the conduction system[19] The endocardium and valves are very rarely involved[2] but I have seen carcinomatous implants on the *mitral valve secondary to a* carcinoma of the uterus and on the tricuspid valve secondary to carcinoma of the gallbladder In general the right side is involved more often than the left side of the heart but the experience of Burnett and Shimkin[18] and of Gassman et al[36] does not accord with this Pericardial effusion is common[14]

Most of the secondary cardiac neoplasms have their primary origin in malignant tumors of the bronchi lungs and breast[85, 21] But the primary neoplasm may be situated in the esophagus mediastinum thyroid uterus genitourinary tract and many other organs[79] Melanosarcoma and carcinoma of the skin not *infrequently metastasize to the heart*[63, 20] I have observed a case of Ewing's sarcoma of bone which had given rise to a cherry sized polypoid metastasis of the left ventricle near the apex

Invasion of the heart by secondary tumors has been said to occur by direct extension from neighboring intrathoracic organs (chiefly bronchi, lungs pleura, thymus, mediastinal glands and tissues) But in the series of cases reported by Prichard,[73] spread by the lymphatic route, retrograde from the tracheobronchial lymph nodes, occurred more frequently than direct invasion, even from carcinoma of the lung The malignant tissue infiltrates the pericardium and may also invade and replace the myocardium Intrathoracic neoplasms may also break into a pulmonary vein, and by passage through the left atrium, left ventricle aorta and coronary arteries reach the cardiac tissues Direct invasion of the heart may result from extension of tumor masses through the inferior vena cava to the right atrium This may be the mechanism in cases of renal hypernephroma and in occasional instances of testicular teratoma, hepatic malignancies and chondrosarcoma Less often cardiac metastases are secondary to malignant tumors in distant organs The malignant cells reach the heart by passage through the blood stream Tumor cells have actually been found in the circulating blood and endocardial vegetations Least commonly secondary neoplasms of the heart result from retrograde lymphatic extension from neighboring intrathoracic organs or lymph nodes

A variety of systemic neoplastic diseases rarely involve the heart in these instances the pericardium is usually involved *The most common of these* are Hodgkin's disease[39, 43, 82] lymphosarcoma[94, illegible] and reticulum *cell* sarcoma[16, 10] and malignant lymphoma[illegible] Invasion of the heart usually follows direct extension, or retrograde lymphatic spread from involved mediastinal lymph nodes I have also observed a thymic lymphosarcoma which infiltrated the parietal and visceral pericardium Like other pericardial sarcomata the lymphomatous lesions of the pericardium are often associated with pericardial effusions which may be hemorrhagic *Occasionally* leukemic infiltrations are found in the pericardium or myocardium Adhesive peri

carditis or pericarditis with effusion occurs frequently when myelogenous or lymphatic leukemia involve the heart ■ Kaposi s sarcoma involving the heart[105] and neurofibromatosis with cardiac involvement have also been reported [74]

CLINICAL MANIFESTATIONS OF CARDIAC TUMORS

Most cardiac tumors produce no clinical symptoms and are discovered only at post mortem examination In some cases of secondary cardiac tumors the symptoms referable to the cardiac metastases are obscured or overshadowed by those of the primary disease Occasionally however both primary and secondary tumors give rise to distinctive clinical features which permit an accurate diagnosis In the latter group symptoms are dependent on the location and to some extent on the size of the tumor Symptoms result from interference with the passage of blood through the heart impaired transmission of the cardiac impulse through the conduction system pericardial reaction or rarely from extensive myocardial damage Somewhat characteristic clinical syndromes may be associated with a few of the individual cardiac tumors

Congestive Heart Failure Symptoms of congestive heart failure are generally regarded as the most common manifestations of cardiac neoplasms These include dyspnea and orthopnea and venous engorgement with or without peripheral edema and serous effusions Careful analysis discloses that these symptoms do not usually represent heart failure caused by extensive neoplastic myocardial damage In some instances the dyspnea results from the primary pulmonary neoplasm while the venous engorgement is the consequence of metastatic involvement of lymph nodes and mediastinal tissues with obstruction of the superior vena cava In others symptoms indistinguishable from heart failure are due to subacute or chronic compression (tamponade) by extensive malignant pericardial involvement with or without effusion [3, 90] But typical manifestations of congestive heart failure may be caused by longstanding functional mitral stenosis due to a myxoma or other polypoid tumor of the left atrium which occludes the mitral orifice Progressive heart failure and sudden death in a case of myxoma of the left atrium have been attributed to pressure on the pulmonary veins [100] Only occasionally is heart failure produced by extensive sarcomatous destruction of the myocardium The heart failure due to cardiac tumors ■ characterized by its intractable rapidly progressive course and its failure to respond to all therapy Its sudden and unexplained development has also been remarked

Chronic cardiac tamponade and superior caval syndrome result from lymphomatous, metastatic or primary malignant neoplasms of the pericardium In some of these cases the onset with cough malaise and fever suggests ■ diagnosis of grippe Later the full clinical picture develops with increasing dyspnea engorgement of the cervical veins enlargement of the liver and small rapid pulse

Weller[105] associated Kaposi s sarcoma of the right atrium with a distinctive syndrome which he believed permitted clinical recognition The onset resembled that of an acute upper respiratory disease which became protracted (cough malaise weakness night sweats and occasional hemoptysis) Edema of the face at first transitory was later striking and permanent Other features were cyanosis fever between 100 F and 101 F and roentgen ray shadow of a mass along the right atrial border with or without evidence of pericardial effusion When a ardiac murmur is present the clinical picture may resemble bacterial endocarditis However these symptoms and signs are not specific and may be encountered with any malignant tumor of the right atrium and with pericardial malignancies which eventually obstruct the superior vena cava

Acute circulatory failure with a shock like syndrome is apt to result from a ball valve tumor of the left atrium which intermittently and increasingly obstructs the mitral valve [65, 49] Transient obstruction of the circulation sometimes associated with change of position in bed may cause attacks of faintness or syncope cold extremities and cyanosis [77] Peripheral cyanosis, localized necrosis of the tip of the nose fingertips and toes or gangrene may result from prolonged intense circulatory obstruction

A huge ball valve thrombus of the *right* atrium in a patient with mitral stenosis and atrial fibrillation was reported to produce dusky cyanosis of the face and neck engorgement and systolic pulsation of the cervical

veins enlargement and systolic pulsation of the liver, air hunger without pulmonary congestion pronounced enlargement of the right heart, especially the right atrium, and rapid variations in the severity of the clinical features [110]

Acute malignant pericarditis or pericarditis with effusion may be evidenced by a friction rub over the precordium or by physical and roentgenologic signs of diffuse water bottle type of cardiac enlargement In several cases of malignant pericarditis that I have observed, a pericardial rub persisted for more than thirty days Symptoms and signs of cardiac tamponade may develop rapidly only after many months Pericardial aspiration may yield a serofibrinous exudate or a sero sanguineous effusion but a 'dry tap' may be encountered because of complete pericardial adhesion When pericardial effusions due to malignancy are aspirated there is a tendency to rapid refilling of the sac Temporary spontaneous resorption of a pericardial effusion may be associated with misleading, transient clinical improvement [13] Pleural effusions, also frequently hemorrhagic, are likely to accompany pericardial effusions because of direct extension of the malignancy to the pleura

Arrhythmias are relatively common The most characteristic are atrial fibrillation and flutter which may appear as transient paroxysms but later persist [33, 4] Paroxysmal tachycardia, frequent premature beats and occasionally heart block or bundle branch block have also been reported Unexplained tachycardia has often been noted The arrhythmias are usually encountered in cases with metastatic neoplasms of the atria especially the right atrium Heart block has been associated with lymphangioendothelioma [3, 56] and hemangioendothelioma[40] of the atrioventricular node with multiple rhabdomyomata and with leukemic infiltration of the interventricular septum [3] Perry and Rogers[70] reported a case of Adams Stokes syndrome with heart block due to cardiac lymphangioendothelioma

Signs of valvular disease usually those of mitral stenosis[57, 3] and occasionally of tricuspid stenosis [96] may be present in cases of polypoid tumor of the atria [5, 34a] Myxoma of the left atrium is the commonest cause of this form of functional valvular stenosis[99] but less commonly a pedunculated sarcoma[47] or metastatic sarcoma is responsible In 1933 Ludwig[57] assembled 21 cases including one of his own in which tumors of the left atrium had caused a functional mitral stenosis Wainwright[10] reported a case of metastatic sarcoma which reached the left atrium and mitral valve and produced signs of mitral valvular disease Cardiac catheterization in cases of right and left atrial myxomata have disclosed elevation of right atrial pressure in the former and of the pulmonary "capillary pressures in the cases of left atrial tumor [6, 55, 44] The cardiac output was diminished at rest or upon exercise

The murmurs may be typical of mitral (or of tricuspid) stenosis or they may be bizarre in quality, location and variability Occasionally in cases of ball-valve neoplasms the murmur varies or disappears with change in the patient's position [52] Syncope on standing or with change of position, periods of coldness and cyanosis of the extremities peripheral embolization, epileptiform convulsions with gangrene of the nose and extremities [5] progressive heart failure unresponsive to treatment, and sudden unexpected death are among the clinical features in these cases notably of myxoma or sarcoma

Sudden death is relatively frequent, especially in primary tumors of the heart This was the mode of exitus in one third of the cases of myxoma or fibroma of the atria and in about three quarters of the rare cases of lymphangioendothelioma It is also common with cardiac rhabdomyomata Sudden death may follow a period of intermittent or persistent circulatory failure, but it also occurs without preliminary circulatory symptoms

A variety of other clinical manifestations may owe their genesis to cardiac tumors *Angina pectoris* and typical manifestations of *coronary artery occlusion* may result from neoplastic involvement or obstruction of the coronary vessels In one of Fishberg's [3] cases continuous cardiac pain for sixteen days was due to a tumor encircling the left circumflex artery Non specific chest pain occurs in cases of pericardial neoplasm Primary or secondary pericardial sarcoma may cause rapid death by rupturing into the pleural cavity I have seen a perforation of the inferior vena cava by a mediastinal chorioepithelioma I have also observed the clinical picture of Laennec's cirrhosis with ascites edema of the lower extremities and dilatation of the veins of the abdominal wall, caused by an adenoma of the

left kidney which extended into the inferior vena cava and up to the right atrium. Post mortem examination revealed also an adherent fibrous pericardium and thrombosis of the hepatic veins. Rarely a myxoma of the left atrium causes embolization and infarction of various organs.[17] Convulsions in cases of cardiac tumor may be due to heart block (Adams Stokes syndrome) or to tuberous sclerosis of the brain associated with cardiac rhabdomyomata. *Congenital rhabdomyomata* may produce cardiac murmurs when the tumors are situated on the valvular leaflets and arrhythmias are not uncommon due to atrial involvement.[103] In addition these cases are characterized by cyanosis at birth and indifference to surroundings; later there is delay in walking and in mental development, epileptiform seizures and sudden death during an apparently minor ailment.

Roentgenologic examination may disclose bizarre irregular protuberances or advanced universal enlargement of the cardiac silhouette with obliteration of the normal cardiac curves. The appearance may resemble that of a pericardial effusion or localized bulges may simulate ventricular aneurysm or pericardial cyst.[[illegible], 34] Immobility of the right border of the heart on fluoroscopy and irregular or unusual cardiac borders may be noted.

Angiocardiography has disclosed filling defects in enlarged atria in cases of atrial myxomata.[6, 91] It may also be helpful in the differential diagnosis of pericardial neoplasms.[4, 18] Polypoid tumors of the left atrium may effect "mitralization" of the cardiac shadow with straightening of the left border and prominence of the left pulmonary salient.

The **electrocardiogram** is not usually distinctive.[89] It may depict atrial fibrillation or flutter due to atrial involvement[33] or rarely heart block[56, 44] or bundle branch block[103] and P wave abnormalities in atrial neoplasms.[97] Elevation of the RS T segments and inversion of T waves in leads I and II were documented by Boman[12] in a case of primary sarcoma of the pericardium. In a case of carcinoma of the esophagus with massive metastases and extensive destruction of the heart muscle, Rosenbaum[81] et al observed persistent upward displacements of the RS T segments in leads II, III, V_F and in unipolar leads. They interpreted these findings which resembled those seen following combined anterior and posterior infarction as being due to continuous acute myocardial injury by invading neoplasm. Although the electrocardiogram in occasional cases of cardiac neoplasm has been mistaken for that of anterior or posterior wall infarction, the characteristic discordant ST elevation and depression of the latter in leads I and III have not been described.

DIAGNOSIS

More than twenty reports have been made of correct antemortem diagnosis, most of them in recent years and usually in cases of secondary (malignant) tumors of the heart.[33, 3, 18, 38] Primary tumors have also been recognized during life by Barnes et al,[7] Popp,[72] Shelburne,[87] Lange and Christiansen,[53] Goldberg et al,[37] Bahnson and Newman,[6] Steinberg et al[[illegible]] and others. Because of the possibility of surgical removal, the recognition of benign tumors is especially important.

As with other rare forms of heart disease, diagnosis depends on alert awareness that cardiac neoplasm may be responsible for cardiac manifestations, especially when the clinical course is atypical. In the presence of a malignant neoplasm elsewhere in the body, especially in the neighboring thoracic organs, certain clinical features should suggest the occurrence of cardiac metastases. These diagnostic features are:

(1) The rapid onset of congestive heart failure without apparent cause and its unabated progression despite treatment.

(2) The development of signs of fibrinous pericarditis or pericarditis without other apparent cause. The pericardial rub, if present, persists for many days or weeks. A blood tinged pericardial tap is confirmatory[67] and the finding of tumor cells is diagnostic.[[illegible], 89]

(3) The occurrence of paroxysmal or persistent atrial fibrillation or of heart block in the absence of the usual causes of these disturbances.

(4) The development of cardiac tamponade as indicated by dyspnea, engorged veins, hepatic enlargement, falling blood pressure and pulse pressure, tachycardia and pulsus paradoxus.

The *diagnosis of primary tumors* is more difficult. Signs of mitral stenosis in the absence of a history of rheumatic fever together with symptoms and signs of ball valve

obstruction of the mitral valve (p 656), should suggest the possibility of a polypoid myxoma fibroma or sarcoma of the left atrium Episodes of syncope, dyspnea or cyanosis which are unexplained except for their relation to change of position may suggest the diagnosis Occasionally an atrial tumor is discovered during an operation for mitral stenosis or constrictive pericarditis Similarly the presence of right atrial tumor may be suggested by a tricuspid murmur intractable congestive right sided heart failure without apparent cardiac or pulmonary disease or evidence of superior vena caval obstruction (edema and cyanosis of the neck and face and venous engorgement with or without dilated collateral veins on the chest wall) Differential diagnosis may require angiocardiography to demonstrate or exclude the presence of a tumor

Primary tumors of the pericardium (teratoma sarcoma) may be recognized by physical signs of pericarditis or pericardial effusion, especially hemopericardium, or by bizarre, localized bulges of the roentgenologic silhouette of the heart Angiocardiography, fluoroscopy and kymography may differentiate these tumors from aneurysms, since the tumors do not fill with Diodrast and pulsation is absent or only transmitted, the latter is not an absolute distinction *Rhabdomyoma* may be suggested by the association of cardiac enlargement cardiac irregularity, and convulsive seizures with or without Adams-Stokes syndrome in backward, mentally deficient infants or children, who may have adenoma sebaceum

Examination of the pericardial fluid in cases associated with pericarditis with effusion may disclose the presence of tumor cells

TREATMENT

Treatment of the secondary neoplasms of the heart is essentially symptomatic Acute cardiac tamponade due to rapidly accumulating pericardial effusion may require frequent paracentesis of the pericardium Rapid relief of alarming circulatory deficiency followed the aspiration once of 340 cc and again of 300 cc of extremely hemorrhagic fluid in a case of metastatic carcinoma of the pericardium reported by Barnes Beaver and Snell[7] Deep roentgen ray therapy may temporarily destroy pericardial neoplasms or lymphomata and effect more or less symptomatic relief as in the case of pericardial metastasis reported by Shelburne and Aronson,[33] and as in the case of Hodgkin s disease of the pericardium reported by Garvin[25] Nitrogen mustard, radioactive P^{32} or urethane therapy may be tried The instillation of radioactive gold (Au^{198}), with a physical half life of 2 7 days, into the pericardial cavity of a patient with massive, recurrent pericardial effusion secondary to carcinoma of the breast was followed by temporary diminution of the effusion, relief of symptoms, and a radiation effect on the neoplasm without significant injury to the myocardium[4]

Hope for surgical removal of primary tumors was engendered by Beck's[9] report of a case of an intrapericardial teratoma and one of tumor of the heart in which the lesions were successfully extirpated and the patients cured Maurer[6] reported the successful removal of a primary lipoma of the heart, weighing 3½ pounds Several attempts have been made at surgical removal of a right or left atrial myxoma diagnosed during life, but almost invariably these attempts have been failures[11 38] But Scannell and associates[6] reported the successful removal of a myxoma from the left atrium, with the aid of hypothermia

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Chapter 46

FUNCTIONAL MANIFESTATIONS REFERRED TO THE HEART

The physician is confronted more often with functional disturbances which the patient refers to his heart than with organic cardiac abnormalities.[3, 11] Proper treatment requires the ability not only to differentiate these functional disorders from organic heart disease but also to recognize them when superimposed on organic heart disease. These functional problems will be discussed under the following headings:

1. Neurocirculatory asthenia or cardiac neurosis
2. Isolated and transient functional cardiac symptoms
3. Objective functional cardiac signs
4. Phobias regarding heart disease
5. Fainting or syncope

NEUROCIRCULATORY ASTHENIA OR CARDIAC NEUROSIS

DEFINITION

Neurocirculatory asthenia (NCA) refers to an ill defined syndrome of psychogenic or neurogenic origin, often mistaken for organic heart disease and characterized by dyspnea, precordial pain, palpitation, exhaustion and a general incapacity or inefficiency in adjusting *to physical or emotional strain.*

Despite the distinctive titles given to this syndrome it is not a nosologic entity. It is nothing more than a moiety of the more general picture of psychoneurosis which in the cases under discussion chances to assume entirely or predominantly the garb of cardiac or circulatory symptoms.[34] Hence the term "cardiac neurosis." DaCosta[10] in 1871 applied the title "irritable heart" but recognized that the manifestations were due to a functional cardiac disorder. "Disordered action of the heart" (DAH) and "soldiers heart"[32] were popular terms during World War I. Parkinson[39] and Lewis[31] employed the synonym "effort syndrome" because the symptoms were readily induced by minor exertion.[2] Oppenheimer and associates[37] first employed the label "neurocirculatory asthenia" to denote a generalized weakness of the circulatory system due more particularly to its innervation but they clearly recognized the importance of the psychoneurotic factor in its causation.

ETIOLOGY AND PATHOGENESIS

Underlying Cause: Psychologic Disturbances

The underlying cause appears to be a fundamental ego insecurity arising from psychologic problems which began in infancy and childhood. In the vast majority of cases a careful history discloses previous serious maladjustments or nervous breakdowns, long absences from school or work, or unexplained prolonged illnesses.[13, 11, 7, 9] The relative importance of constitutional (genogenic) factors and of psychic factors in producing neurocirculatory asthenia is undetermined.

That psychologic disturbances frequently present their "somatic" extension into the cardiac sphere is not surprising. The heart is the traditional center of emotional expression. *There is an early awareness of* changes in cardiac activity with the strain of physical and emotional activities.[5] Literally and figuratively life and its emotions are symbolized in the beat of the heart and death in its stoppage. Death fears and death wishes are psychologically interwoven in the maladjusted person and the heart is an appropriate site for their somatic expression. Finally, accidental factors often determine the cardiac localization of psychoneurotic disturbances, e.g., the inadvertent remark of a physician, rejection of an application for life insurance, news of cardiac disease or of the cardiac death

of a relative, friend, neighbor or prominent person or the experience of palpitation or precordial discomfort

Physiologic Mechanism

In recent years physiologic methods have been applied to the study of functional disorders of the heart and an effort has been made to interpret these disorders in terms of pathologic physiology [5, 1] The similarity of the manifestations of neurocirculatory asthenia to those associated with stimulation or inhibition of the sympathetic and vagal nervous system suggested that the syndrome was due to autonomic imbalance "[29] On the basis of clinical and experimental data a more primary origin of the "autonomic imbalance" is postulated in the hypothalamic region and the latter is conceived as being functionally disturbed by abnormalities in cortico hypothalamic control [III] Since the hypothalamus is a center for the mediation of numerous endocrine and metabolic as well as autonomic nervous functions the concept of an hypothalamic origin of neurocirculatory asthenia is at best a non specific one A hypothalamic disturbance can be assumed with equal propriety for gastrointestinal and other visceral functional disturbances as well as for a host of so-called psychosomatic diseases

NCA and Hyperventilation The Hyperventilation Syndrome

The similarity of certain symptoms of NCA to those of hyperventilation [3] suggested that the latter was a major factor in the production of functional cardiac manifestations [40] However it has been amply demonstrated that these symptoms usually appear in the absence *of hyperventilation, and the latter is merely* one and only an occasional one of the manifestations of the underlying psychologic or neural disturbance [50]

Conversely hyperventilation may produce a clinical syndrome characterized by neurovascular, muscular respiratory, gastrointestinal and psychic, as well as cardiac manifestations [III] The cardiac and respiratory manifestations of the hyperventilation syndrome, viz palpitation, tachycardia atypical chest pain together with fatigability, faintness and breathlessness have certain resemblances to those of neurocirculatory asthenia but other features due to hyperventilation are lacking in the latter

NCA and Graves Disease

Because of a resemblance of functional cardiac symptoms to some of the symptoms of hyperthyroidism, NCA has been interpreted as an earlier and larval form of Graves' disease [35] This relationship has not been demonstrated for any significant number of cases

Extrinsic Factors—Relation of War and Strain

Neurocirculatory asthenia is predominantly a disorder of civil life, but it appears in a more striking form and has been studied most extensively among soldiers during war As in previous wars the outbreak of World War II was soon followed by the publication of numerous studies of NCA [31, 41, III] I have indicated that the fundamental cause of NCA is a psychologic insecurity and maladjustment but the onset of overt symptoms, as with all psychoneurosis, is usually precipitated by some extrinsic environmental strain War presents a particularly intense life strain with removal from family and friends dislocation of environment and activity new competitive situations close exposure to severe physical exertion intense anxiety and fear as well as risk of death In civilian life the symptoms of neurocirculatory asthenia are likewise precipitated by stress producing life situations associated with fear anxiety anger, frustration and despair [49, 4] However, these are rarely as intense as those presented by intimate and prolonged exposure to the actual hazards of war The more serious the intrinsic psychiatric difficulty the less severe is the external factor needed to precipitate symptoms Conversely even the so-called normal individual may exhibit functional cardiovascular symptoms if the environmental strain is extremely intense and prolonged

Age

In its overt form neurocirculatory asthenia is said to occur most commonly between the ages of 20 to 40 but this is largely a matter of terminology It may occur at any age

Sex

In civilian life it is much more common among females than among males

Heredity

Functional cardiovascular or other psychoneurotic symptoms are common among the parents and siblings of patients with neurocirculatory asthenia There appears to be a high family incidence of neurocirculatory asthenia

Infections

Acute infections have often been arraigned

as precipitating causes of NCA. Although this relationship is possible not only physical factors but complex psychologic ones may be involved. Sometimes maternal or familial overprotection and overanxiety during a childhood illness set up a pleasant subconscious association with ego importance and exaggerated parental attention. Often this initiates abnormal anxieties regarding illness and a withdrawal from physical exercise, especially active sports. With subsequent illnesses the pattern both of anxiety and prolongation of disability tends to recur.

CLINICAL FEATURES

Symptoms

Dyspnea is usually the commonest and most distressing symptom. It generally occurs at rest and is described as an inability to take a deep breath and not as a panting such as follows exertion. There is often an irregular sighing which is readily demonstrable in the curve of a basal metabolism test. The incidence and severity of the dyspnea are disproportionate to the degree of exercise and to the objective disturbances in ventilation.[3]

There are occasionally spontaneous attacks of dyspnea and tachypnea which have been described as the hyperventilation syndrome. They have been interpreted as a psychogenic expression of the fear of suffocation, especially in patients with claustrophobia.[48] These outbursts are often associated with tachycardia, giddiness, axillary and palmar sweating, and anxiety and may culminate in frank tetany.[illegible] Patients with NCA and respiratory symptoms exhibit a diminished capacity for breath holding.[50]

Pain in the precordium is usually distinctive from that of angina pectoris. It may be a dull continuous ache or soreness or may be sharp, intermittent and dartlike. The pain is usually localized to the region of the apex of the heart, the nipple or inframammary area. It is either unrelated to effort or occurs some time *after* a tiring exertion. Unlike the pain of angina pectoris it does not compel the patient to stop activity nor is it rapidly relieved by rest. Occasionally there is an associated local precordial tenderness which may be abolished by the infiltration of procaine. The precordial pain of NCA has been attributed to excessive use and tonic spasm of the intercostal muscles.[50] This explanation is based on the observation that patients with functional cardiovascular disturbances tend to breathe almost exclusively with their chest wall and not with their diaphragm.[50, 18]

Palpitation occurs commonly. As a rule there is an uncomfortable awareness of the heart beat in the absence of any arrhythmia. But tachycardia and a forceful cardiac pulsation are often present. Occasionally premature beats or paroxysmal tachycardia account for distressing cardiac discomfort, pain and intense anxiety.

Fatigability is a characteristic feature of neurocirculatory asthenia. It takes two forms. One is a sense of great fatigue on arising in the morning which gradually diminishes in the course of the day's activity. The other is a profound exhaustion following relatively minor physical exertion. In severe cases of NCA the patient spends many hours in bed during the day as well as at night.

Psychic symptoms characterized by phobic, depressive and hypochondrial elements have been described by Badal.[4]

Fever of mild degree is not uncommon in civilian practice; it often presents great difficulty in diagnosis and management. The temperature rarely exceeds 100.5 and is often discovered after a mild sinusitis or respiratory infection. Often it is the physician who initiates cardiac symptoms by diagnosing rheumatic fever and advising prolonged bed rest.

Other symptoms which are included in the syndrome of NCA are dizziness, sweating, cold clammy palms, nervousness, tremor, headache, flushing, frequency of micturition, insomnia, paresthesia, faintness, diarrhea, difficulty in concentration, indecision, impairment of memory and a tendency to mental, emotional and physical apathy.

Objective Signs

There are no objective signs of organic cardiac disease as a rule. But patients with NCA may independently experience rheumatic, coronary (atherosclerotic) or other cardiac disease. Furthermore the discovery of such organic heart disease may be the factor which precipitates overt symptoms of NCA.

The electrocardiogram is usually normal.[47] In some patients there is a depression or inversion of the T wave in leads II and III and in precordial leads.[3] More often the T waves are normal when the patient is recumbent and abnormal when he sits or stands. The fact that

these postural electrocardiographic changes may be minimized or abolished by ergotamine suggested that they are due to sympathetic stimulation [illegible] The heart tends to be small, but it is normal when related to the size of the thorax and body [15, 6]

Tachycardia is common not as a result of effort but because of emotional attitudes [27] Following exercise the pulse rate increases more than normally and its return to the original level is abnormally delayed The blood lactate concentration is significantly higher in NCA during moderate exercise than in control subjects [7] The vital capacity is normal but there is an increase in minute respiratory volume [8]

DIAGNOSIS

The diagnosis of NCA is based on the general appearance and behavior of the patient, on an analysis of the above mentioned symptoms and on the exclusion of organic heart disease But the diagnosis should also be made when NCA is combined with organic heart disease by a similar analysis of the symptoms and by recognition of the lack of relationship to the type and severity of the organic disease The diagnosis of neurocirculatory asthenia should be made not only by exclusion of organic cardiac disease but also by positive data supporting the psychologic basis of the symptomatology

A *hyperventilation test has been suggested* to aid in diagnosis [17] The duration of breath holding after hyperventilation, divided by the duration of breathholding before forced breathing is termed the hyperventilation index Normally it exceeds 1 3 In patients with NCA who have respiratory symptoms it is less than 1 3 Its value remains to be assessed

DIFFERENTIAL DIAGNOSIS

Neurocirculatory asthenia is not infrequently treated as rheumatic fever, sinusitis, undulant fever, tuberculosis and hyperthyroidism It is especially important not to misinterpret the symptoms as being due to organic heart disease

PROGNOSIS

The outlook for disappearance of symptoms and for efficient work is poor when there is a serious psychiatric background a long history of symptoms and when the syndrome of NCA appears after relatively brief and minor strain On the other hand a good symptomatic result may be anticipated if the syndrome appears acutely, after a prolonged and very intense emotional and physical strain in an individual without previous significant psychomotor or personality derangement If the precipitating cause can be discovered and abolished, it is probable that the symptoms can be alleviated

Follow up studies of cases of NCA are difficult to evaluate and compare because cases are not analyzed according to the above mentioned factors and because of differences in criteria of improvement or cure Grant [1] studied 601 former soldiers with NCA about seven years after discharge Approximately 15 per cent were free of symptoms another 15 per cent improved, and over 50 per cent unchanged or worse Relatively poor results were reported by Parkinson [illegible] and by Jones and Lewis [27] whereas others reported remarkable therapeutic results as measured by the percentage of patients returned to military duty [43, 19, 26]

TREATMENT

Winning and retaining the patient's confidence and cooperation are essential This is usually accomplished by a careful and detailed history and physical examination and the demonstration of a complete understanding of and interest in the patient's symptoms Reassurance as to the absence of organic heart disease is invaluable The recommendation of rest is to be avoided While it may provide the solace that comes from the avoidance or escape from life's situations, it usually fosters *the very factors responsible* for the disorder

Specific treatment should be directed toward the underlying psychologic abnormality and toward the extrinsic factors which appeared to precipitate the syndrome [illegible] When the latter occurs acutely as a result of an obvious extreme harrowing experience reassurance as to the circulatory status and elimination of the precipitating cause are usually curative In other acute cases without previous profound psychologic difficulties the precipitating factor is less obvious and must be sought by repeated discussions or by narcohypnosis if necessary Elimination of the precipitating factor when possible and guidance of the patient in management of his problem or in his adjustment to it often yield a favorable result

In chronic cases the discovery and control or removal of the precipitating factor are likewise helpful but it is desirable and often essential that the total life situation of the patient and his attitudes and emotional reactions be analyzed A revision in the patient s standards and goals which are retained from infancy and childhood is often valuable An effort should be made to enhance his ego security by lowering his exaggerated and anachronistic standards by increasing his self evaluation and by promoting his physical and intellectual capacities and his social relationships

Treatment of individual symptoms is secondary but important Beneficial results have been attributed to the judicious use of sedatives vitamins sex hormones and occupational therapy as well as to reassurance and reeducation Reeducation should involve the formulation of and guidance in a program of physical mental and social activity best suited to the individual s particular problems capacities and needs

ISOLATED AND TRANSIENT FUNCTIONAL CARDIAC SYMPTOMS

Under this heading are included cases in which isolated functional symptoms such as difficulty in taking a deep breath precordial pain or palpitation occur in an individual without apparent psychologic difficulties As a rule he is annoyed by the symptom and may be worried about the presence of heart disease but his efficiency at work and his interpersonal social relationships appear unimpaired

In such cases reassurance as to the normalcy of the heart and the functional nature of the symptom often suffices to alleviate it or to render the patient unconcerned Sometimes a change in hygiene including more sleep and relaxation a holiday a bland diet and regular bowel habit and elimination of tobacco alcohol and coffee are helpful especially for palpitation or submammary pain Local infiltration with procaine may eliminate pain at least temporarily and convince the patient that it arises in the chest wall and not in the heart Physical exercise including training in abdominal (diaphragmatic) breathing is valuable in patients with functional dyspnea If the symptom is severe and persists despite these measures a more fundamental psychiatric investigation and treatment are necessary

OBJECTIVE FUNCTIONAL CARDIAC SIGNS

Under this heading are included systolic murmurs arrhythmias tachycardia or minor electrocardiographic abnormalities which cannot be related to any underlying organic disease Tachycardia [illegible] paroxysmal tachycardia[4] and heart block[4, 11] have been related to precipitating emotional factors These have been discussed in connection with the above mentioned individual conditions Careful cardiac investigations and follow up examinations are essential to exclude organic disease If evidence of organic disease is absent it is best to emphasize this to the patient, to reassure him and to avoid restriction of activity On the other hand insurance examiners are often compelled to reject such individuals for insurance or to increase their premium rates on the purely statistical basis of a greater than expected mortality rate

HEART PHOBIAS

This includes three types of cases (1) fear of cardiac death although there are neither symptoms nor signs of cardiac disease[9] (2) fear of cardiac death because of functional symptoms or signs or (3) fear of cardiac death because of actual organic heart disease Sometimes symptoms referable to the heart or a fear of heart disease are the result in part or in toto of words or actions of the physician Such an anxiety neurosis has been termed *iatrogenic heart disease*[15] However the iatrogenic factor should not be overemphasized since there are usually more fundamental constitutional and/or psychologic underlying causes[illegible]

The first group presents a purely psychiatric problem and should be so handled In the second and third groups the therapeutic mainstay is reassurance as to either the absence of heart disease in group (2) or as to the favorable outlook if the patient in group (3) follows the physician s instructions In all groups avoidance of unnecessary restrictions as to physical activity supports the physician s verbal reassurance

FAINTING AND SYNCOPE

These have been discussed in Chapter 12 They are mentioned here because many people associate fainting with cardiac disease However cardiac disease is responsible for only a small minority of cases e g , Adams-

Stokes syndrome Although emotional factors, especially fear and anxiety may induce the common type of vasodepressor faint, there is often no profound psychologic difficulty If the stimulus such as the sight of blood or an operation is repeated several times, the syncopal response may no longer occur In many of the patients subject to occasional faints of the vasodepressor type there appears to be a defect of vasomotor regulation

Hysterical fainting has been distinguished by the absence of objective changes in blood pressure pulse or electroencephalogram The fainting is due to a deep seated psychologic disturbance

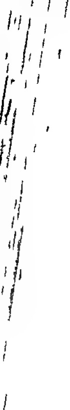
Hyperventilation may produce giddiness and a faint feeling but no syncope except indirectly by inducing anxiety and a vasodepressor reflex [12]

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PART VII

SPECIAL PROBLEMS IN HEART DISEASE



Chapter 47

PREGNANCY AND HEART DISEASE

Pregnancy is a physiologic process which imposes a functional load on the heart and circulation. Pregnancy is well borne by the normal heart, which calls upon its substantial reserve to supply the increased demands of the growing embryo. The response of the diseased heart, on the other hand, is not always adequate and varies with the degree of cardiac compensation before pregnancy. The well compensated heart may tolerate the increased circulatory demands of pregnancy essentially as well as the normal heart under the same circumstances; hearts with limited reserve fail with significant frequency. Thus pregnancy is not responsible for a specific etiologic type of heart disease. But in the presence of a previously diseased heart, pregnancy may represent an intolerable circulatory burden which induces cardiac failure and death.

Preexisting heart disease has been generally regarded as the most important complicating factor likely to endanger the otherwise smooth course of normal pregnancy and labor, but this may no longer be accurate since cardiac complications are being avoided or treated more effectively.[illegible] According to Hamilton,[42] *heart disease was present in 1.8 per cent of 76,125 pregnancies* treated at the Boston Lying-In Hospital in the past twenty-five years. In other studies the incidence of heart disease in pregnant women varied between 1 and 7 per cent.[44, 84, illegible, 42, 1] Heart disease in pregnancy almost always means rheumatic heart disease. The latter is encountered in over 90 per cent of pregnant cardiac patients; congenital cardiovascular lesions occur in 1.5 to 5 per cent, whereas syphilitic, hypertensive and other types of heart disease are observed only occasionally.[6, illegible, 42, 11, 56] Among the rheumatic cardiac cases, mitral stenosis alone or in combination with aortic valvular disease occurs in at least 75 per cent

PATHOLOGIC PHYSIOLOGY OF THE CIRCULATION IN PREGNANCY

Oxygen Consumption and Basal Metabolism. The circulation in pregnancy provides an increased volume of blood necessitated by the growing embryo. The latter augments the total metabolism of the body and consequently the *consumption of oxygen*. According to Cohen and Thomson[30] the *consumption of oxygen* increases between 15 and 25 per cent, owing almost entirely to the uterus and its contents.[17] But since this approximates the average weight change during pregnancy, they concluded that the *basal metabolic rate* was essentially unchanged. On the other hand, Clute and Daniels[28] stated that the *basal metabolic rate* in normal pregnancy was elevated as much as 25 to 30 per cent. Watrous and Blakely[67] found a slight progressive rise in basal metabolism during pregnancy and a maximal increase of 5 to 25 per cent at the tenth month.

Cardiac Output. The cardiac output (minute volume) increases progressively *from the third or fourth month to the twenty-fifth to the thirtieth week, at which time it is usually about 30 to 50 per cent above normal.*[37, 8, 20, 71, 45, 2, 8] In the last 8 to 10 weeks of pregnancy there is a moderate fall in the cardiac output from these maximal levels. The cardiac output falls to prepregnancy levels about two weeks post partum. In part, the augmented output is mediated by a slight acceleration of the pulse rate (10 to 20 beats per minute), but in large measure it is due to a greater output per beat (elevated stroke output). The increase in cardiac output is greater than the increase in oxygen consumption. The arteriovenous oxygen difference is diminished.

Work of the Heart. The work of the heart is proportional to the product of the cardiac output and the mean arterial blood pressure

Since the latter [redacted] not usually altered during pregnancy[47, 3] the work of the heart per beat and per minute are increased by as much as the cardiac output namely up to about 50 per cent[87] This additional work may represent the extent of the cardiac load of pregnancy

Circulation Time The augmented cardiac output reflects a similar enhancement of the venous return to the heart The latter is accomplished in part by an acceleration of the speed of the circulation and in part by an enlargement of the circulating blood volume There [redacted] a progressive acceleration of circulatory speed (reduced circulation time) from the third to the ninth month of pregnancy This acceleration diminishes moderately in the last weeks before term[29] While there are discordant reports regarding the circulation time[88, 60, 28] the findings of Cohen and Thomson[29] have been confirmed by those of Manchester and Loube[redacted] whose determinations in 48 pregnant women disclosed a progressive circulatory acceleration from an average circulation time of 12 4 seconds in the first trimester to 10 2 seconds in the third trimester

Blood Volume Recent studies using T 1824 dye[2] radio-iron[24] or P^{32} labeled red cells[7] have yielded results somewhat at variance with those previously reported[94] Nevertheless, there appears to be a progressive rise in blood and plasma volume beginning about the thirteenth week of pregnancy reaching a maximum about the thirty second week, and diminishing thereafter The peak increase in blood volume is about 30 per cent, in plasma volume about 40 per cent and in erythrocytes about 20 per cent The red cell volume may continue to increase to term[24]

Since the plasma volume increases proportionately more than the cell volume there is a diminished viscosity and hematocrit which may account for an apparent slight anemia

Total body water like plasma volume increases progressively but unlike the latter its volume rises until the end of pregnancy[41, 53]

Sodium retention is an important feature in pregnancy The normal total exchangeable sodium was found to average 39 3 milliequivalents per kilogram There was an average absolute increase of 20 mEq per week or a total of 500 mEq during the second and third trimesters The increment in exchangeable sodium could be accounted for by the uterus and its contents and the expanded blood volume[40] The retention of sodium and water in pregnancy has been related to the increased activity of the adrenocortical sodium retaining hormone, aldosterone Its secretion rises sharply after the third month of pregnancy and remains at a high level up to term[95] Following delivery it declines speedily to pre pregnancy levels

SIGNIFICANCE OF CIRCULATORY CHANGES

The circulatory changes in pregnancy have been interpreted [redacted] similar to those of an arteriovenous fistula[16] There is an almost direct connection between arteries and veins in the placenta[85] The consequent blood shunt from the arterial to the venous side results in an acceleration of blood flow, of venous return and of cardiac output Some support for this concept was found in observations of the circulatory dynamics during and after labor by Brown and her associates[redacted] but there are many gaps in the analogy between the circulatory changes in pregnancy and those in cases of arteriovenous fistula

The circulatory adaptations in pregnancy may be likened also to those of hyperthyroidism in that in both they are designed to satisfy increased metabolic demands—local demands in pregnancy generalized in hyperthyroidism In both increased metabolism results in accelerated velocity of blood flow, which is, however, much less pronounced in pregnancy The increased speed of circulation is insufficient to maintain the required cardiac output in pregnancy and the progressive augmentation of blood volume may be regarded as a compensatory mechanism to provide a needed increase in cardiac output The cardiac output increases substantially more than the oxygen consumption[19] because of a subnormal arteriovenous oxygen difference, the latter [redacted] probable consequence of the accelerated speed of circulation

While the increased circulating blood volume and the augmented venous return are thus viewed as adaptive mechanisms their disadvantages must also be considered Like exercise, saline infusions and other factors which enhance the venous return, the load of pregnancy imposes no serious strain on the normal or well compensated heart The diseased heart with diminished functional reserve, may be unable to maintain an adequate cardiac output despite the enlarged blood volume Further increases in blood

volume cannot be normally propelled by low-reserve hearts The consequence is a congestion of the lungs viscera and other tissues behind the failing chambers Since the accelerated blood flow the augmented blood volume venous return cardiac output and work of the heart all become significantly greater after the third or fourth month and reach their maximum in the eighth lunar month the intervening period represents the span of increasing danger to the cardiac patient There is in fact a close correlation between the time of onset of heart failure and the severity of the circulatory load [84]

CIRCULATORY DYNAMICS OF LABOR

As compared with the prolonged and increasing strain of pregnancy that of labor is relatively well tolerated Nevertheless it does represent a strain comparable to that of muscular exercise The oxygen consumption rises during labor [81] Slight tachycardia occurs during the actual delivery and bradycardia post partum Labor is associated with a moderate transient elevation in arterial blood pressure and a corresponding increase in the work of the heart [81] It has been noted that the blood volume cardiac output and work of the heart diminish significantly in the eight weeks before term whereas the fetus continues to enlarge and the oxygen consumption red cell mass and total body water continue to increase up to term After labor there is a further reduction in blood volume and a considerable fall in body water associated with marked diuresis A rise in venous pressure in the first 24 hours after delivery has been attributed to the effects of Ergotrate [13] That the strain of normal labor is less than that of pregnancy is supported by the infrequency of heart failure beginning during or immediately after delivery On the other hand if heart failure is present when labor starts there is a great risk of intensifying the myocardial insufficiency This is particularly likely to occur in the first 24 to 48 hours post partum

CARDIOVASCULAR MANIFESTATIONS DURING PREGNANCY

An evaluation of the cardiac status should take into account the frequency of cardiac symptoms and signs in pregnant women even without heart disease These may simulate the manifestations of organic heart disease and heart failure [84]

Dyspnea at rest and on exertion and orthopnea are common complaints especially in the latter half of pregnancy The dyspnea may be due to increased respiratory effort to ventilate the deflated lung of pregnancy Often the dyspnea of pregnancy takes the form of sighing respiration or of inability to take a deep breath a disturbance of psychic origin In any event neither exertional dyspnea nor orthopnea is to be regarded as certain evidence of heart failure without careful evaluation

Ventilation and Lung Volumes Careful studies have disclosed that the vital capacity remains unchanged or increases slightly during the course of pregnancy [93] The inspiratory reserve is increased the expiratory reserve and residual volume slightly decreased [17] Breathing is performed with the lungs chiefly in the expiratory position However although the vital capacity is normal or only slightly increased the minute volume ventilation is greatly increased [4] According to Cugell et al [4] ventilation increases somewhat in the first trimester and progressively thereafter to a maximum increase of about 42 per cent at the tenth month The increment in ventilation exceeds that of oxygen consumption indicating that the pregnant woman hyperventilates at rest This inefficiency may be due to increased work necessary to ventilate the deflated restricted lung of pregnancy

Palpitation and tachycardia are frequent with or without associated dyspnea Respiratory distress choking sensations and palpitation occurring at night may simulate an attack of paroxysmal nocturnal dyspnea But cough with frothy or blood stained sputum and pulmonary rales are not noted There may be transient basal rales due to compression of the lung by the elevated diaphragm but these disappear after cough or a few deep respirations

Edema of the legs develops in about 25 per cent of non cardiac pregnant women especially during the last two months of pregnancy The association of dyspnea and edema is likely to suggest the possibility of heart failure But the edema is a local phenomenon confined to the lower extremities It is due to compression of the iliac veins by the enlarged uterus and its contents While an extremely high venous pressure in the lower extremities is probably the chief cause of the dependent edema the enlarged circulating blood volume

a diminished concentration of blood proteins and of osmotic pressure, and local tissue changes may be contributory factors That the edema is not due to heart failure may be perceived from the absence of venous engorgement in the cervical veins and from the normal venous pressure in the upper half of the body

Cardiac enlargement may be diagnosed because the apical impulse is displaced to the left and upward by the elevated diaphragm Roentgenologic observations disclose displacement of the heart upward laterally and forward as pregnancy advances, owing chiefly to elevation of the diaphragm and to lordosis The transverse diameter of the heart may thereby be increased These findings suggest cardiac enlargement but the area and volume of the heart increase only in proportion to an increase in the corresponding dimensions of the chest [9] Allowance should be made for the tendency to overestimate the size of the heart on physical examination and the difficulties of such examination due to the enlarged breasts Hollander and Crawford [9] were impressed by the cardiac indentation of the anterior wall of the esophagus

A *systolic murmur* is audible at some time during pregnancy in most women Usually it is in the pulmonic or apical regions Diastolic murmurs should be considered as evidence of organic heart disease unless proven otherwise A third heart sound is frequently audible and may simulate the gallop rhythm of heart failure The second pulmonic sound is often loud and may be accentuated and reduplicated especially in the third trimester A slight tachycardia is the rule with the highest cardiac rate in the eighth month Premature beats are not uncommon and may be associated with palpitation Paroxysmal atrial tachycardia is being reported with increasing frequency during normal pregnancy [9, 91] The *arterial blood pressure* is often unchanged during pregnancy, or there may be a reduction in the diastolic blood pressure with a consequent increase in pulse pressure A collapsing pulse and capillary pulsation may accompany a wide pulse pressure in the absence of aortic valvular disease

The *electrocardiogram*[93] usually shows a left axis deviation and an inversion of T_3[22] in the first two trimesters These are due to the transverse position of the heart and resemble the findings in the electrocardiogram of obesity A deep Q_3 as well as the inverted T_3 is encountered in a small percentage of cases and is probably due also to the altered position of the heart [22, 60] *Vectorcardiographic changes* in pregnancy[15] are similarly related to positional changes

DIAGNOSIS OF CARDIAC DISEASE IN PREGNANCY

The recognition of organic heart disease when present, is essential for the proper management of the pregnant woman Due care must be taken not to mistake the above-mentioned findings in pregnancy for cardiac disease

Often a careful history will reveal that the patient has some organic cardiac lesion and simple physical and fluoroscopic examination readily confirms this information But occasionally a previous diagnosis of heart disease may be found to be inaccurate On the other hand, the absence of a history of rheumatic fever or the failure of previous routine examinations to disclose a cardiac disease should not be accepted as proof that the heart is normal

Since the common heart disease of pregnancy is rheumatic heart disease careful search should be made for evidence of mitral or aortic valvular disease The crescendo presystolic murmur of mitral stenosis may be overlooked unless the patient is examined *in* the left lateral (decubitus) position preferably after exercise The murmur may be sharply localized to the apex The diastolic murmur of aortic insufficiency is often best heard along the left sternal border with the patient standing and with the breath held in expiration A loud systolic murmur may be due to rheumatic aortic stenosis a systolic thrill should be sought carefully *In its absence* pulse tracings may confirm the diagnosis

Fluoroscopic examination may provide the first clue or the confirmatory evidence of heart disease Cardiac enlargement *should* be unequivocal to be diagnostic in itself The localization of the enlargement *may* be especially significant, e g , the left atrium and the pulmonary salient in mitral stenosis and the left ventricle in association *with* dynamic pulsations of *the ventricle* and aorta in cases of aortic insufficiency

The possibility of *congenital heart disease* should be considered The machinery like

murmur of a patent ductus arteriosus is distinctive Coarctation of the aorta may be suggested by the presence of hypertension or an unexplained loud systolic murmur especially in the left posterior chest Subaortic stenosis may be suggested by a loud aortic or pulmonic systolic murmur and thrill since infancy and by left axis deviation in the electrocardiogram Tetralogy of Fallot has rarely been encountered in pregnancy, but more patients with this condition may live to maturity and become pregnant following the Blalock or Potts operation

In summary the recognition of cardiac disease in pregnancy requires a careful physical, fluoroscopic and electrocardiographic examination A diastolic murmur and distinct cardiac enlargement are the chief diagnostic features The cardiac enlargement is most suggestive if it involves distinct contours of the heart which can then be related to corresponding valvular lesions and murmurs In the presence of loud systolic murmurs, a diagnosis of organic heart disease depends on confirmatory findings such as thrills, unequivocal cardiac enlargement or collateral evidence of congenital heart disease

DIAGNOSIS OF HEART FAILURE

Having distinguished the cardiac patient in pregnancy, the physician must evaluate the functional capacity of the heart and make careful observations to recognize promptly the development of heart failure

In practice a careful history of the patient's exercise tolerance as determined by her response to various activities in her daily life is a useful guide to the functional capacity of the heart Her ability to consummate a previous pregnancy and labor successfully is an important index of cardiac capacity Since dyspnea and orthopnea occur during pregnancy without heart disease their usual merit as early clues of heart failure is somewhat vitiated Nevertheless, by careful history and observation the physician may justly conclude that the dyspnea is out of proportion to that attributable to pregnancy and is in fact caused by heart failure Unexplained cough especially that which occurs on effort is also a valuable early clue to the possible occurrence of heart failure Breathlessness may awaken the patient from sleep or may occur after intercourse The association of cough with frothy or blood tinged sputum and with persistent rhonchi or moist râles in the chest denotes that the dyspnea and cough are due to left sided heart failure Relief of the dyspnea and the cough following extreme restriction of salt and one or two injections of mercurial diuretics is a valuable diagnostic test to confirm the diagnosis of heart failure

Objectively heart failure may be first discovered by serial determinations of vital capacity which is normal in uncomplicated pregnancy In the presence of pulmonary congestion due to left sided heart failure there is usually an unequivocal reduction in vital capacity Although the determination of vital capacity has many limitations it is of value if the patient is intelligent and cooperative and has been taught to perform the test and if successive tests are compared at regular intervals Nevertheless it is not a practical routine procedure As a rule the earliest sign of congestive heart failure is the development of persistent rales at the bases of the lungs The lungs should therefore be examined regularly and carefully in all cardiac patients throughout pregnancy *Prolongation of the circulation time* with or without elevation of the venous pressure is a valuable indication of the presence of heart failure

Of course there is usually no difficulty in determining the presence of heart failure when the complete clinical picture is unfolded The patient is dyspneic on the slightest exertion or at rest Complete recumbency is intolerable because of respiratory distress Mild or moderate cyanosis is common in patients with mitral stenosis and heart failure Râles are readily audible throughout the lower portions of the lungs Hydrothorax may be present The cervical veins become engorged The liver is enlarged and tender Edema of the lower extremities is pronounced

PROGNOSIS OF CARDIAC DISEASE ASSOCIATED WITH PREGNANCY

Rheumatic Heart Disease

The prognosis of heart disease in pregnancy is essentially that of rheumatic heart disease Pregnancy involves a greater risk for the cardiac patient than for the normal individual However with increasing knowledge and attention to the problems of the cardiac patient the mortality rate during pregnancy has been substantially reduced From quoted figures

of 40 to 55 per cent mortality at the turn of the century, the rate dropped to 15 per cent in the first three years after the formation of the Heart Clinic at the Boston Lying In Hospital in 1921, to 5 per cent between 1925 and 1927 and to 2 or 3 per cent between 1937 and 1939 [44] The over all maternal death rate among cardiac patients in the past twenty five years was 3 9 per cent There were 17 deaths (4 8 per cent) among 352 cardiac patients carried through pregnancy and for two years post partum by Jones,[46] and only 29 deaths among 3000 pregnant cardiacs reported by Mendelson [57] These mortality figures apply essentially to rheumatic heart disease which accounts for 90 per cent or more of heart disease in pregnancy

Although the maternal death rate is still about five times as high as among non cardiacs it is perhaps as important to emphasize the 97 or 98 per cent chance of survival among cardiac patients who are pregnant as to stress the greater risk among these patients Furthermore the mortality rate among pregnant cardiacs should be compared with that of non pregnant cardiacs in the same age range for the expected mortality among cardiacs is higher than that of non-cardiacs, independent of pregnancy It appears likely that if the obviously decompensated patient is restricted from becoming pregnant and if the compensated cardiac patient is carefully managed to avoid heart failure during the course of pregnancy or is properly and promptly treated if heart failure does develop, then the maternal mortality rate among pregnant cardiacs need not significantly exceed that among non cardiac pregnant individuals nor that among comparable cardiac patients who are not pregnant [84]

The prognosis among cardiac patients during pregnancy conforms remarkably with that anticipated on the basis of cardiac functional classifications made at the onset of pregnancy Utilizing the functional classification of the New York Heart Association, Pardee[72] observed the following mortality in the various classes

Class I Patients with organic heart disease who suffer no limitation of activity There were no deaths among 157 patients in this category

Class II A (now Class II) Patients with heart disease who suffer slight or moderate limitation of activity There was 1 death among 180 patients in this group

Class II B (now Class III) Patients with heart disease who experience moderate to great limitation of physical activity Less than ordinary physical activity causes discomfort There were 8 deaths among 169 such patients

Class III (now Class IV) Patients with heart disease who are unable to carry on any physical activity without discomfort There were 16 deaths among 40 such patients

These and other observations indicate that pregnancy is tolerated without significant additional risk by the well compensated patient with heart disease but that the mortality rate increases as the degree of compensation diminishes Carr and Hamilton[21] and Hamilton and Thomson[44] found that an unfavorable outcome might be anticipated among those cardiac patients who present (1) signs of heart failure or a history of heart failure (2) a serious disorder of the heart beat such as atrial fibrillation, (3) a complicating serious disease such as diabetes pulmonary tuberculosis, nephritis Among 95 cases classified as "unfavorable' on the basis of these criteria, when first seen the maternal mortality rate was 16 7 per cent in contrast with a mortality rate of 2 3 per cent among 655 cases which were classified as "favorable because they did not satisfy these criteria Patients with atrial fibrillation suffered the notably high mortality rate of 33⅓ per cent However, it is doubtful whether atrial fibrillation per se is necessarily associated with a high mortality rate in pregnancy Atrial fibrillation denotes a late stage in the life history of rheumatic heart disease and is usually a precursor of or is accompanied by, heart failure The outlook in patients with atrial fibrillation is determined chiefly by the *functional capacity* of the heart and the absence or presence of heart failure It is chiefly because of pregnancies among cardiac patients with poor cardiac reserve or actual heart failure that the maternal mortality is relatively high among subjects with heart disease

If the patients who develop congestive heart failure during pregnancy labor or the puerperium are omitted from consideration it is doubtful whether pregnancy has any ultimate deleterious effects on longevity or mortality rates [84, 10] The studies of Friedberg and Tartakower[35] and of Reid[77] indicate that

if the pregnancy itself is well tolerated there is no shortening of the life of cardiac patients even after bearing many children

Congestive heart failure is the commonest serious complication of pregnancy in cardiac patients and the most frequent cause of death[11, 44] [illegible] Its likelihood of occurrence is greater the less the cardiac reserve of the patient as evaluated at the onset of pregnancy Cardiac failure occurs more frequently in cardiac patients who become pregnant after the age of 35 than in those below that age level The incidence of heart failure increases sharply after the fifth month of pregnancy and progressively thereafter to the eighth or ninth month corresponding to the similar increase in physiologic strain as described above With the reduction in circulating blood volume and cardiac output in the last eight weeks of pregnancy there is a corresponding diminution in the occurrence of heart failure According to Gorenberg and McGleary[37] 80 per cent of 77 cases of heart failure developed before the last month of pregnancy Acute heart failure beginning during the course of labor is uncommon but heart failure that is already present may be intensified The majority of deaths from heart failure occur during the puerperium but careful history and observation disclose that the onset of heart failure in such instances usually occurred during the course of pregnancy

Of the other complications of pregnancy in cardiac patients *subacute bacterial endocarditis* is one of the most important[33, 46] The early use of penicillin or penicillin and streptomycin in adequate dosage should minimize the mortality from this disease The maternal mortality during pregnancy in 85 patients with healed bacterial endocarditis and 35 patients cured of this disease during pregnancy was 6 6 per cent[72] Following recovery from bacterial endocarditis the outlook during a subsequent pregnancy is dependent on the functional status of the heart without regard to the history of the endocarditis But it is generally advised that at least six months should elapse following cure before childbearing is again undertaken

Pulmonary embolism infection toxemia and hemorrhage are complications in non cardiac as well as cardiac patients although embolism may occur more frequently in the latter With the inauguration of early ambulation and the use of anticoagulants the frequency of and mortality from pulmonary embolism may be sharply reduced Postpartum infection has already diminished as a cause of death since the use of antibiotics

About half of the cases of *dissecting aneurysm of the aorta* in women under 40 occur during the course of pregnancy

The importance and frequency of *activation of rheumatic fever* in pregnancy[37, 3, 51] has been greatly exaggerated There are no reliable data to indicate that pregnancy activates rheumatic fever Clinically active rheumatic fever is very rare during pregnancy although febrile episodes in the pregnant woman with rheumatic heart disease are erroneously attributed to rheumatic fever Rheumatic fever may be observed occasionally in pregnant women in their teens particularly when there has been rheumatic activity within the preceding two years

Congenital Cardiac Disease

Pregnancy and labor have been successful in many patients with congenital heart disease[64, 3] including those with interatrial or interventricular septal defects[80] congenital heart block[6, 74] patent ductus arteriosus[48] pulmonary stenosis coarctation of the aorta[47, 73, 79] tetralogy of Fallot[3, 4] and truncus arteriosus communis [illegible] There are insufficient data to permit a detailed discussion of each lesion in pregnancy In patients with septal defects or a patent ductus with left to right shunt there may be a dangerous or fatal reversal of shunt after the uterus is emptied The functional capacity of the heart and the presence or absence of cyanosis and heart failure rather than the specific lesion are generally the determining factors in the outlook for pregnancy and labor in women with congenital cardiac lesions In cases of coarctation of the aorta there is a particular *danger of vascular accident (ruptured cerebral aneurysm)* or dissection of the aorta attributed to a rise in blood pressure during pregnancy and labor[34, 63, 78] Miller and Falor[67] recommend that the coarctation be corrected surgically early in pregnancy But if the patient is first seen late in pregnancy a cesarean section should be performed and surgery undertaken subsequently Pregnancy may be undertaken safely after the coarctation is corrected Of some interest is the probability that the woman with congenital heart disease

is somewhat more likely to bear an infant with a congenital cardiac lesion than the mother with acquired heart disease

Hypertension and Nephritis Myocardial Infarction

Patients with chronic glomerulonephritis without azotemia and patients with mild essential hypertension assume only a slight risk with pregnancy Patients with severe hypertension and significant cardiac enlargement and those with azotemia assume a risk equivalent to that of patients with unfavorable rheumatic cardiac disease [5, 80] In addition there is some evidence that hypertensive patients have a higher than normal incidence of preeclampsia and eclampsia and that the progress of hypertension is hastened by pregnancy [48, ■] (See also Toxemias of Pregnancy on p 952) Attacks of paroxysmal dyspnea or pulmonary edema with extreme rise in blood pressure may necessitate an interruption of pregnancy but extreme restriction of sodium and fluids the administration of morphine, rest digitalization and diuretics may prevent or control the attacks

Cases of coronary occlusion followed by pregnancy with successful termination have been reported by Horwitz and associates [53] and others [12, 65] Coronary occlusion is a rare event during pregnancy, but 15 cases have been reported with survival in 13 [62] The two patients who developed myocardial infarction in the third trimester died

Arrhythmias

In the presence of persistent or frequent and annoying arrhythmias, quinidine or procaine amide may be administered, without any additional risk because of the pregnancy

FETAL MORTALITY

Among the hazards that cardiac disease adds to pregnancy is the *higher fetal mortality* than among normal pregnant women In the Boston Lying In Hospital the fetal mortality among favorable cases in ten years[42] was 8 6 per cent However among unfavorable cardiac cases the infant mortality was still relatively high at 31 per cent while among patients with atrial fibrillation the infant mortality was about 50 per cent According to Stromme and Kuder,[89] maternal heart disease does not adversely affect infant mortality but no detailed analyses are presented But Bunim and Rubricius[14] found that the infant mortality rate for their group of patients with congestive heart failure was three times ■ high as for patients with compensated heart disease and four times as high as for normal pregnant women delivered on the same obstetrical service Fetal death was found to be significantly increased among mothers with hypertension [98] The chief cause of infant mortality among cardiac patients is prematurity and stillbirth Some of this is due to the unwise practice of interrupting or inducing labor before the thirty fifth week From the viewpoint of the child as well as the mother the risk of labor diminishes in the last month of pregnancy There ■ evidence also that infant mortality ■ less when delivery occurs through the pelvis than when cesarean section is performed [27] The use of low forceps instead of entirely spontaneous delivery may also diminish the risk to the infant [9]

THE MANAGEMENT OF HEART DISEASE AND HEART FAILURE IN PREGNANCY

The major problem in the treatment of the cardiac patient during pregnancy is the prevention and control of heart failure [■] To this end it is essential that the presence of cardiac disease be recognized early The subject with such disease must be registered with her physician early in pregnancy and regular visits at one- or two week intervals should be made depending on her cardiac status and symptoms Cooperation with a cardiologist or with an internist interested in the problems of cardiac disease in pregnancy is desirable Cardiac patients should enter the hospital one to two weeks before the expected date of delivery for proper appraisal of the cardiac status planning of delivery procedure and for *the institution of* treatment of incipient heart failure if necessary

The precipitating causes of heart failure include acute infections especially those of the upper respiratory tract, overexertion and excessive sodium intake These should be avoided as far as possible Antibiotics should be administered promptly at the onset of infections If excessive anemia is discovered it should be corrected Arrhythmias should be treated speedily Sudden weight gain should be regarded as probably due to excessive water retention, and should be treated by more rigid restriction of sodium intake and by mercurial diuretics

The well compensated cardiac patient (Class I and some in Class II) requires little

restriction in activity except for severe and unusual physical exertions A rigid restriction in sodium intake appears desirable especially after the fourth calendar month A moderate restraint in weight gain also appears advantageous Digitalis is not given as a prophylactic measure in this group of patients In these as in all other cardiac patients excellent hygienic care including adequate periods of rest and of sleep attention to proper dietary intake and especially the avoidance of upper respiratory and other infections should be stressed A supplementary intake of vitamin B_1 may be necessary because of the added requirements of pregnancy and the possible contributory role of thiamine deficiency in heart failure

Cardiac patients whose outlook is less favorable because of a poorer cardiac reserve (Class III and some in Class II of the New York Heart Association) or those with a previous history of congestive heart failure require greater restrictions as to physical activity and more rigid regulation In some instances modified bed rest most of the day or rest in a chair or chaise longue may be necessary throughout pregnancy The intake of sodium should be reduced to 500 mg or less daily if possible Digitalis should be continued if started during a previous episode of heart failure Patients in this group of limited cardiac reserve should be hospitalized at least two weeks before term according to the requirements of the individual case Patients in Class III or IV usually require digitalization

If heart failure develops in any patient or is already present when the patient is first seen active treatment should be instituted as described above (Chapter 11) Bed rest at home or preferably in the hospital is necessary Digitalization should be effected and maintained Sodium intake should be restricted to 200 to 500 mg daily Mercurial diuretics should be administered every two to seven days according to the need and response If there is evidence of infection thiamine deficiency anemia or hypoproteinemia which might contribute to the development of heart failure these factors should be eliminated or corrected by appropriate measures The intravenous introduction of fluids containing sodium (saline plasma blood) should be avoided

In the presence of heart failure during the first three months of pregnancy the patient should be aborted by dilatation and curettage after treatment to control the heart failure In cases of heart failure noted later in pregnancy labor should not be induced until after seven calendar months have elapsed i e until after the fall from the peak of the circulatory burden It is unnecessary to terminate pregnancy before term in order to avoid the strain of labor since heart failure rarely begins in labor and since the strain of labor is less than that of pregnancy in the seventh calendar month Cesarean section may be desirable at term in patients with coarctation of the aorta

CARDIOVASCULAR CORRECTIVE SURGERY DURING PREGNANCY

Mitral Commissurotomy

This procedure has been performed in pregnant women with mitral stenosis and has been followed by a successful outcome of the pregnancy[4, 31, [illegible], 35, 44] It would be difficult to prove that the course of pregnancy would have been less favorable with proper medical treatment but without the operation Patients in Class I or II in whom the operative risk of mitral commissurotomy [illegible] low are the patients who are subject to minimal risk from the pregnancy itself and therefore require no prophylactic surgery Patients in Class III and IV in whom pregnancy may be associated with significant mortality are the ones in whom there is a substantial operative risk from mitral commissurotomy It remains to be proved that this operative risk is justified by the reduction in mortality from pregnancy itself effected by the operation If mitral commissurotomy is eventually desirable it is probable that it can be performed with less danger after the stress of pregnancy is over Furthermore it is uncertain how soon after the mitral commissurotomy sufficient clinical improvement will ensue and whether this will occur early enough to be of benefit during the pregnancy The frequent occurrence of the post-commissurotomy syndrome (p 675) points to the probable risk that this will develop before the completion of pregnancy and hamper its course If there is an error in the evaluation of the degree of associated mitral regurgitation the patient will be subjected to an operation which endangers rather than benefits the pregnant woman with cardiac disease

The question of performing a mitral com

missurotomy for mitral stenosis during pregnancy is most likely to arise when there are frequent recurrent attacks of pulmonary edema or refractory congestive heart failure If these conditions are present during the first trimester despite expert treatment, it is best to interrupt the pregnancy and perform a mitral commissurotomy some weeks or months later If these conditions develop after the third month or if the patient with these complications is first seen after that period vigorous medical treatment should be carried out and almost always will permit completion of the pregnancy without operation But if these manifestations of heart failure do not respond to meticulous treatment, a mitral commissurotomy may have to be performed if the evidence indicates that there is a very tight mitral stenosis[67] If pregnancy is interrupted during the first trimester because of severe heart failure, sterilization by tubal ligation is not necessarily indicated because a mitral commissurotomy may be performed later with a good chance of a subsequent successful pregnancy

Correction of Congenital Cardiovascular Lesions

As in cases of mitral stenosis pregnancy proceeds favorably in cases of congenital heart disease which are properly managed, and correction of the lesion should be deferred if possible until after pregnancy is completed Occasionally correction of a coarctation of the aorta has been performed during pregnancy for fear of a dangerous rise in arterial blood pressure during pregnancy or labor Section of a patent ductus arteriosus during pregnancy has been suggested for fear of a reversal of shunt after delivery But except in the presence of heart failure patients with a patent ductus do well during pregnancy A Blalock procedure may be performed in the pregnant patient with tetralogy of Fallot[70]

CONDUCT OF LABOR

Labor should be permitted to proceed normally in the cardiac patient During labor and delivery the patient should be propped up as high as is necessary and feasible Vaginal delivery is allowed even in patients with serious heart disease unless there are non cardiac indications for cesarean section Even in the presence of heart failure it is uncertain that a cesarean section with sterilization should be preferred to delivery from below with sterilization at a later date if desirable The present trend is definitely against interruption of pregnancy in the later months of pregnancy and against cesarean section during labor, for both the maternal and fetal mortality rates are significantly less when normal delivery by the vaginal route is permitted[64, 33] However it is desirable to avoid a prolonged second stage by the use of the low forceps procedure The pulse and respiratory rate and blood pressure should be followed continuously during labor According to Mendelson and Pardee,[48] the elevation of the pulse rate above 110 and of the respiratory rate above 24 during the first stage of labor provide usually reliable clues to impending heart failure and the need for appropriate therapeutic measures, such as digitalization and oxygen therapy Intravenous fluids should be given very cautiously and slowly, if at all during labor The fluid should contain no sodium The patient should be adequately sedated with barbiturates, morphine or Demerol

The competent administration of anesthesia by an experienced anesthetist is important in minimizing the strain of labor Ether is generally regarded as one of the safest anesthetics and is well tolerated by cardiac patients Maximal concentrations of oxygen should be given with it Ethylene and oxygen may be employed only for the preliminary induction of anesthesia but even then the most diligent care should be taken to avoid asphyxia Cyclopropane with oxygen and chloroform have been shunned by many Low spinal or continuous caudal anesthesia have come to be preferred by many especially in patients with actual or impending heart failure

Careful observation should not be relaxed immediately after delivery The rapid onset of acute pulmonary edema or more gradual congestive heart failure may occur during the third stage or at any time in the first 24 hours after delivery Some physicians apply tourniquets prophylactically during the third stage of labor on all patients who have shown previous evidence of heart failure Penicillin 600 000 units and streptomycin 2 gm daily, should be given prophylactically during the third stage and continued for three days postpartum to avoid bacterial endocarditis Ergotrate should not be given Pituitrin should be avoided, but, if essential, only the oxytocic

fraction (Pitocin) should be administered intramuscularly. After delivery an adequate period of bed rest should follow with care as to sodium intake and necessary medication.

Acute pulmonary edema is a sudden and sometimes startling incident which occurs sufficiently often during pregnancy or labor to require special mention. It is usually a complication of mitral stenosis and may occur in apparently well compensated patients and without apparent cause. But often it is induced by the intravenous administration of fluids.[74] Acute and terrifying dyspnea with or without cyanosis, cough, frothy sputum and hemoptysis are the outstanding manifestations. Recurrences during the course of pregnancy are not uncommon.

The prompt administration of morphine may in itself control the attack. The slow intravenous administration of 0.25 to 0.5 gm. (3¾ to 7½ grains) of aminophylline in 10 to 20 cc. of 5 per cent glucose in distilled water may also abort the attack. Digitalis or ouabain should be given intravenously (p. 262). Venous tourniquets should be applied to all four extremities and if this is ineffective a venesection should be performed. Oxygen should be administered by mask or tent under positive pressure if there is no evidence of shock. Antifoaming agents such as ethanol administered by oxygen aerosol may be beneficial.[88] Rarely a rapid venesection is necessary if other measures fail to control the pulmonary edema. If shock occurs, Wyamine (mephentermine) may be given at once intravenously and intramuscularly (p. 564) and a continuous infusion of Levophed set up (p. 563).

To prevent recurrences of pulmonary edema sodium intake should be curtailed drastically, digitalization should be maintained, aminophylline rectal suppositories (0.5 gm. aminophylline) should be inserted before retiring and mercurial diuretics administered at appropriate intervals. The prophylactic use of morphine in the twelve hours following labor may prevent the occurrence of post partum pulmonary edema.

INDICATIONS FOR DISCOURAGING PREGNANCY AND FOR PERFORMING THERAPEUTIC ABORTION

The physician is frequently confronted with the question of advising women with heart disease whether they may safely undertake pregnancy and childbearing or whether they may continue if already pregnant. Often there are associated religious, socioeconomic and personal factors which may be decisive regardless of medical considerations. The physician's advice should consist chiefly in providing his patient with the known data as to prognosis, especially as applied to her own cardiac status. Having been apprised of the facts, she herself must decide whether her desire for a child outweighs the probable risk.

In summary, pregnancy may be undertaken by the well compensated cardiac patient with only slightly more risk than by the normal woman. The mortality risk during the childbearing age is essentially identical for the compensated cardiac patient whether she becomes pregnant or not. In borderline cases she is more justified in undertaking pregnancy if it is the first or second than if there are already two or three children. Pregnancy should be undertaken and the family completed relatively early in life since the diseased heart becomes less capable of tolerating the load of pregnancy with advancing years. However, the woman with rheumatic heart disease who marries before she is 21 might advantageously delay pregnancy for two or three years since the risk of activation of a quiescent rheumatic infection diminishes progressively after the age of 21.

Patients whose outlook is relatively unfavorable (i.e., those in Classes III and IV of the New York Heart Association Classification, or those with signs or a history of heart failure, atrial fibrillation or a complicating serious disease) should be impressed with the considerable risk of pregnancy: maternal mortality of 15 to 18 per cent, fetal mortality of 30 per cent according to data which were accumulated prior to the more effective management of heart failure in recent years. If pregnancy is nevertheless undertaken, the importance of early and constant cardiac supervision and of rigid adherence to a prophylactic and therapeutic regimen must be stressed.

If the problem is one of terminating rather than of undertaking pregnancy, advice varies according to the duration of pregnancy and to religious and legal considerations, as well as the clinical status of the patient. The number of cardiac patients in whom the interruption of pregnancy is clearly indicated is growing progressively smaller. Although the risk to life among well compensated patients is

only slightly enhanced by pregnancy, under special circumstances abortion by cervical dilatation and curettage is permissible during the first two months if the patient desires to terminate the pregnancy This is particularly advisable if there are already three or more children or if the responsibilities involved in raising a family are likely to endanger the patient's health After the first two or three months of gestation the risk of artificial termination of the pregnancy is probably greater in the well compensated cardiac patient than is the completion of term and delivery

Among 'unfavorable' cases i e, with evidence of cardiac failure, termination of pregnancy should be encouraged if the patient is seen in the first three months of pregnancy and a satisfactory control of heart failure cannot be rapidly effected Interruption can be done from below in the first two months or by abdominal hysterotomy if absolutely necessary from the third to the fifth month Thereafter the risk is less if the patient is treated for her cardiac disability and allowed to go to term But even in this unfavorable group, the religious ethical or personal beliefs of the patient may be such that pregnancy is continued despite the risks entailed

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Chapter 48

SURGICAL PROCEDURES IN THE CARDIAC PATIENT

FUNCTIONS OF THE CARDIOLOGIST

An evaluation of the cardiovascular status is a traditional prerequisite to a contemplated major surgical procedure involving a general anesthetic. Implicit in such precaution is the belief that a major surgical operation and general anesthesia impose an unusual strain on the circulation, and that the diseased heart is more vulnerable to this strain than the normal heart. The internist or cardiologist is therefore frequently called preoperatively, not only to determine the cardiac status and whether the patient actually has heart disease but also if a cardiac lesion is present, to advise whether this lesion alters the decision to operate. If an operation is undertaken, the cardiologist may participate in the management of the patient preoperatively, during the operation and postoperatively.

Primarily the surgeon and the patient are interested in the ability of the diseased heart to withstand the proposed operation. An estimate of this ability requires a knowledge of the risk added by the cardiac disease to the usual risk of the operation itself. The cardiologist must also estimate the general outlook and life expectancy of the patient in terms of his cardiac disease. For a substantial surgical risk cannot be justified if the cardiac condition precludes a sufficient survival period to enjoy the benefits of the surgical procedure.

The cardiologist must give consideration to the surgical condition as well as to the cardiac status, for occasionally he will discover that the so-called "surgical condition" is actually a "medical" manifestation of the diseased heart, e.g. abdominal manifestations of myocardial infarction, rheumatic fever or subacute bacterial endocarditis. The dangers of the disease for which operation is being proposed and the disability due to the disease must also be carefully assessed, for an evaluation of surgical risk to a cardiac patient assumes significance only by balancing this risk against the risk and disability if operation is withheld. Finally, aside from the surgical condition itself, the particular procedure which is contemplated, the available facilities and the skill of the surgeon and anesthetist are variable factors which must be estimated before the surgical risk to a cardiac patient can be properly evaluated. Small differences in morbidity and mortality rates with different surgeons or operative procedures on the noncardiac patient may become strikingly exaggerated in the patient with heart disease.

When the decision to operate on a cardiac patient has been made, the cardiologist may be helpful in reducing the surgical risk by the correction or alleviation of heart failure or by other preoperative measures. He may also be consulted on the choice of anesthetic agents and on circulatory problems which arise in the course of operation and postoperatively. In many operations, particularly those on the heart, his presence and cooperation during the surgical procedure and recovery are highly desirable or essential.

In general it may be stated that the cogency of the surgical indication is usually more important than the cardiac status in determining whether an operation should be performed. In the vast majority of cases the cardiac lesion is no contraindication to a necessary operation. For practical purposes the compensated heart which permits a reasonably normal if somewhat restricted way of life is virtually as capable of handling a major operation and a general anesthetic as a normal heart and the surgical mortality rate is *not* substantially higher.[66, 15] In the presence of heart failure or other serious manifestations of heart disease

however the evaluation of the surgical indication as against the surgical risk often presents a difficult problem

CIRCULATORY RISKS IMPOSED BY SURGICAL PROCEDURES

The commonest surgical risks which may adversely affect the diseased circulation are hemorrhage and shock infection and thromboembolism When these complications are severe and uncontrolled they are equally fatal in the cardiac and non cardiac patient In borderline cases however the presence of cardiac disease may turn the tide against recovery

Cardiac hypertrophy is the usual compensation for many forms of cardiac disease The effectiveness of this compensation depends on the maintenance of an increased supply of oxygen and nutriments to the enlarged heart by way of the coronary vessels Hemorrhage is a serious threat to this compensatory mechanism because it may adversely compromise cardiac nutrition and oxygenation Degrees of myocardial anemia which could be tolerated by the normal heart might result in irreversible and serious myocardial damage or in fatal cardiac disturbance when the heart is already enlarged or suffering from advanced coronary artery disease Furthermore hemorrhage is a common cause of surgical shock with its attendant hypotension The hypotension reduces the coronary blood flow an occurrence which is distinctly less well tolerated by the diseased and enlarged heart than by the normal heart Similarly shock due to other surgical causes besides hemorrhage (p 305) poses a greater hazard for the heart with valvular coronary or myocardial disease

Aseptic technique and the availability of modern chemotherapeutic and antibiotic measures have greatly reduced the incidence and dangers of postoperative infection but such infection has not been entirely eliminated, and the cardiac patient is more apt to suffer or succumb than the patient with a normal heart Infection is one of the common precipitating causes of heart failure in the cardiac patient

Thromboembolic disease following operations is a serious hazard to all patients but it occurs with much greater frequency among those with heart disease than among non cardiac patients (p 959) Furthermore theoretical considerations and clinical experience indicate that thromboembolic complications are more apt to cause serious circulatory disturbances or death in the cardiac patient

Despite the greater hazard of these surgical complications to the cardiac patient it must be emphasized that their incidence is relatively low and not much higher in the cardiac than in the non cardiac patient The severity of the complication itself rather than the presence or absence of heart disease usually determines its clinical outcome For these reasons when proper care and skill are employed the additional cardiac strain imposed by a surgical operation is only infrequently of decisive importance

CARDIAC RISKS IMPOSED BY ANESTHESIA

Only when chloroform was used was the danger of anesthesia dependent in part on the possibility of cardiac damage by direct action of the anesthetic on the heart muscle As a rule however the risk of anesthesia is related to the danger of hypoxemia cardiac (vagal) reflexes accumulation of carbon dioxide (hypercarbia) sharp changes in blood pressure and the induction of cardiac arrhythmias [43]

Hypoxemia may result from the low oxygen concentration in the anesthetic mixture or from chemical or mechanical causes interfering with respiration or the respiratory airway The damaged enlarged heart especially the heart with diminished coronary reserve is particularly susceptible to hypoxemia which may induce myocardial necrosis or predispose to ventricular fibrillation and cardiac arrest

Cardiac standstill or ventricular fibrillation may occur during the induction of anesthesia or during the operative procedure Tachycardia bradycardia extrasystoles and other arrhythmias may be associated with anesthesia (infra) These complications are more likely to occur in patients with certain types of cardiac disease especially those with severe coronary atherosclerosis calcific aortic stenosis or syphilitic coronary ostial stenosis

A sharp reduction in blood pressure such as often accompanies spinal anesthesia may seriously impair the coronary blood flow in susceptible cardiac or hypertensive patients Hypotension may result from large doses of barbiturates or from the inhalation of anesthetics if the anesthesia is deep since

these agents cause marked peripheral vasodilatation The excitement and struggling associated with the induction of anesthesia may increase the work of the heart not only by elevating the blood pressure but also by causing an increased outpouring of nor epinephrine The latter may be especially detrimental to patients with low coronary reserve Hypertension may be due to improper depth of anesthesia, to hypoxia or to abnormal accumulation of carbon dioxide, caused by airway obstruction, improper pulmonary ventilation or inadequate absorption by soda lime

THE TYPE OF OPERATION

There are insufficient data to permit statistically valid generalizations as to the added risk of associated heart disease in various individual operative procedures However the reported observations in relatively small series of cases as well as personal clinical experience are the bases for the following impressions and opinions

Minor Procedures

Such procedures as are usually performed with local procaine anesthesia on ambulant patients in the physician s office or in the outpatient department of a hospital can usually be performed on cardiac patients of all types without significantly greater risk than on noncardiac patients Most dental extractions are included under this heading provided that multiple extractions are not performed at one sitting Even multiple simultaneous extractions may be permissible under certain circumstances in well compensated cardiac patients But in the patient with valvular lesions multiple extractions at one time predispose to bacterial endocarditis

Operable Malignant Neoplasms

These almost always demand early surgical intervention if there is a chance of cure and the cardiac condition is not in a terminal stage

Emergency Operations

Operation is essential regardless of the presence of heart disease if the surgical condition is one which is otherwise rapidly fatal Such conditions include certain forms of acute and massive hemorrhage, perforation of a viscus cases of acute cardiac tamponade not relieved by medical means, strangulated hernia, acute phlegmonous appendicitis, ovarian cyst with torsion of the pedicle, and certain mechanical forms of acute intestinal obstruction

Acute suppurative or gangrenous cholecystitis may also be included in this category of emergency operations but conservative treatment is sometimes warranted if careful observation discloses regression of clinical features The use of antibiotics may eliminate some of these cases from the category of surgical emergencies, especially when there is associated cardiac disease

Peripheral embolism usually denotes underlying cardiac disease Despite the added risk due to the latter, a surgical attempt to remove the embolus is indicated if it involves a major artery and threatens gangrene or death

Elective Operations

It is not always certain whether a contemplated operative procedure is essential or elective When it is elective the ordinary risk of the operation plus the added risk due to associated cardiac disease must be weighed against the risks and discomforts of conservative treatment and the disability due to the unoperated surgical condition

Urinary obstruction due to prostatic hypertrophy and other urologic diseases are among the commonest conditions in cardiac patients for which operation is performed[81] The surgical and cardiac risks are further complicated by the relatively advanced age of these patients which averages between 65 and 70 years Coronary (atherosclerotic) heart disease is very frequent in these patients Postoperative coronary occlusion is relatively common In a series reported by Morrison[72] the mortality rate for various forms of prostatectomy or suprapubic cystotomy averaged 19 per cent in 125 operations on cardiac patients as against 7 5 per cent in 823 such operations on non cardiac patients

As a rule prostatectomy for prostatism is indicated in cardiac patients only if there are episodes of complete obstruction if there is severe retention with secondary infection or impairment of renal function or if frequency, nocturia or overflow incontinence is intolerable Transurethral resection appears to be the operation of choice when the surgeon is skilled in this procedure and the estimated weight of the prostate does not substantially exceed 50 gm In patients with advanced heart failure or minimal outlook for life repeated catheterization or an indwelling

catheter and the use of antibiotics may be preferable to operation But when the surgical indications are clear cut the surgical risk must be considered relatively moderate in most cardiac patients Among other urologic conditions occasionally demanding operative intervention despite coexisting cardiac disease special mention may be made of urinary calculus with obstruction

Operations on the Biliary Tract The urgent surgical indication in most cases of acute suppurative or gangrenous cholecystitis has been mentioned Obstructive jaundice due to a common duct stone almost always demands surgical intervention but delay is sometimes justified either to confirm the diagnosis or in patients with serious cardiac disease to await the possibility of spontaneous passage of the offending calculus or calculi

Cholelithiasis and chronic cholecystitis which are only discovered by roentgenologic examination and are virtually asymptomatic are probably best treated by moderate dietary restriction If there are severe persistent symptoms especially frequent attacks of biliary colic despite medical treatment cholecystectomy is usually clearly indicated even in the presence of cardiac disease If the patient is relatively young and the cardiac disease well compensated a cholecystectomy may be desirable even if the symptoms are fairly well controlled by onerous dietary restrictions Under such circumstances the risk of early cholecystectomy may be less than that of delaying the operation and being forced to do it when the patient is much older and the cardiac status much less favorable In a study of 100 patients with coronary heart disease subjected to cholecystectomy the surgical procedure was well tolerated and there were no deaths or other serious complications on the operating table There were 3 postoperative deaths 2 of which were due to pancreatitis or pancreatic necrosis

Other common elective operations in cardiac patients include hernioplasty and hemorrhoidectomy These operations are usually well tolerated by cardiac patients unless there are serious cardiac complications Therefore if the disability of the hernia hemorrhoids or other elective surgical condition is great the operation should be performed before advancing age and the progress of the cardiac disease greatly enhance the risk If the cardiac status is poor and the operative indication is not compelling conservative therapeutic measures should be employed

Thyroidectomy for hyperthyroidism has hitherto been essential in cardiac patients even in the presence of heart failure Although the results were usually brilliant the operative mortality was substantially greater than in non cardiac patients with hyperthyroidism (p 1012) Therefore at the present time treatment should be carried out with radioactive iodine followed by a brief period of lugolization until the radioactive iodine becomes effective Similarly in cases of fibroid uterus with excessive bleeding radiotherapy should be employed instead of hysterectomy if there is serious heart disease

Cardiac operations have been discussed in connection with the individual lesions The safe conduct of the patient through cardiac surgery has been discussed by Black and Harken[51] Poor cardiac function or congestive heart failure is no contraindication if the operative procedure is designed to diminish cardiac strain or promote aeration of the blood This applies to release of the heart in constrictive pericarditis to correction of a patent ductus arteriosus or arteriovenous aneurysm or to the amelioration of tetralogy of Fallot or advanced mitral stenosis or other such conditions Correction of such lesions as coarctation of the aorta patent ductus or arteriovenous aneurysm is justified by the unfavorable natural course of these conditions

THE TYPE OF CARDIAC DISEASE AND FUNCTIONAL CARDIAC STATUS

The surgical indication is usually a more important factor than the presence or absence of heart disease in deciding upon an operative procedure But insofar as cardiac disease adds to the surgical risk both the status of cardiac function and the etiologic type of heart disease are determining factors In general there is statistical evidence to indicate that rheumatic heart disease is associated with a lower mortality than coronary heart disease or syphilitic cardiovascular disease[13, 71]

Rheumatic Heart Disease

The risk of surgical procedures in rheumatic patients resembles that of pregnancy in such patients in that there is a close correlation to the functional state of the heart (p 1092) The well compensated rheumatic cardiac patient tolerates surgical operations virtually as well as the normal individual[64] The risk

rises substantially in those who have experienced an attack of heart failure or those who are suffering from heart failure at the time of operation [72] A careful clinical history with special reference to dyspnea, cardiac asthma and orthopnea, exercise tolerance and previous episodes of heart failure is essential for a satisfactory evaluation of cardiac function Cardiac operations are being performed regularly and successfully in patients with heart failure, e g, in patients with mitral stenosis Nevertheless although the indication justifies the risk, the mortality does increase in cases of moderately severe or advanced heart failure

Patients with calcific aortic stenosis are susceptible to sudden death a danger which may be increased by a general anesthetic or surgical procedure The risk is greatest in those patients who have experienced dizziness, syncope or angina pectoris The surgical mortality rate also rises in cases of rheumatic heart disease when the patient passes the age of 35 for developing coronary atherosclerosis often impairs the blood supply required to maintain compensation by the enlarged heart Rheumatic cardiac patients are susceptible not only to the more general risks of surgical operations but also to a complicating bacterial endocarditis The latter is most likely to follow dental operations and operations on the genitourinary tract

Hypertension

Operative procedures are tolerated virtually as well by patients with uncomplicated hypertension as those with normal blood pressure Among other evidence to support this opinion is the minimal operative mortality associated with extensive sympathectomies even in cases of malignant hypertension However, the surgical risk in most major operative procedures on hypertensive patients increases when there is evidence of cardiac insufficiency, severe coronary disease, renal impairment or a previous cerebral accident In the presence of these complications operation is permissible only when the surgical indication is absolute

Coronary Heart Disease

The surgical risk is somewhat higher with coronary artery disease than with other cardiac diseases Therefore it is especially important that the surgical indication be unequivocal However, it is important to emphasize that major surgical operations are well tolerated by the great majority of patients with clinical coronary disease provided adequate measures are taken to prevent myocardial ischemia [■] Preoperative emotional anxiety and excitement, hypoxia shock and deep anesthesia must be avoided Brumm and Willius[14] reported only 11 cardiac deaths (4 3 per cent) among 257 patients with severe coronary artery disease undergoing major operations The mean age of these patients was 60 years There was a history of previous myocardial infarction in 32 and a history of angina pectoris in the remainder In another series of 517 patients with coronary heart disease subjected to major and minor operative procedures, there was a mortality of 2 9 per cent in comparison with a mortality of 2 0 per cent among a control group of non cardiac patients who underwent similar procedures [■] Cardiac disease was responsible for a mortality of 1 2 per cent among the coronary patients and only 0 1 per cent among the non cardiac patients However patients with previous myocardial infarction may experience a relatively high incidence of cardiorespiratory complications, such as fresh myocardial infarction, bronchopneumonia, pulmonary embolism or congestive heart failure Such complications are most likely to occur in patients with prolonged operations marked cardiac enlargement or previous or present heart failure [41]

Frank heart failure increases the surgical risk in patients with coronary disease as it does in rheumatic patients but the close correlation with degree of functional impairment is absent The risk of myocardial ischemia and the danger of postoperative myocardial infarction or of sudden death due to ventricular fibrillation or other cause are complicating factors

Surgical risk is greatly enhanced if operation is performed in the course of a recent myocardial infarction Therefore an electrocardiogram should always be taken preoperatively to exclude recent myocardial infarction On occasion, I have observed such routine electrocardiograms to reveal that myocardial infarction was responsible for the acute abdominal symptoms which were interpreted as due to an acute abdominal surgical complication Unless there is an acute emergency demanding immediate operation, surgical procedures should be delayed at least three months following the acute myocardial in

farction. If there is a history of increasing frequency of angina pectoris or of its occurrence with less and less provocation, an impending coronary occlusion is probable and operation should be avoided or delayed if possible.

Bundle Branch Block and Heart Block

These conditions in themselves are not contraindications to a surgical operation, but the underlying cardiac disease and associated manifestations must be evaluated.[73] *In 51 major and 107 minor operations on 56* patients with an average age of 67 years whose electrocardiograms showed bundle branch block, there were no fatalities, but postoperative shock occurred in 16.[86] The association of *Adams-Stokes syndrome* with heart block adds greatly to the risk of operation and the latter should be performed only for emergencies. Patients with asymptomatic fixed heart block usually tolerate surgical *procedures. But patients with first degree* heart block may be more susceptible than normal subjects to the hazard of complete atrioventricular dissociation and ventricular standstill during anesthesia or surgical stress.[84]

Chronic Atrial Fibrillation

Surgical procedures do not significantly increase the morbidity and mortality in patients with chronic atrial fibrillation if the underlying cardiac disease is adequately compensated. Finkbeiner and associates[35] reported an operative mortality of 5 per cent in 60 patients with cardiovascular disease associated with chronic atrial fibrillation who underwent 76 major operative procedures. But there were cardiovascular complications during operation in 71 per cent of the 76 procedures and cardiopulmonary complications in *22 per cent. Only 23 per cent* were uncomplicated. A high incidence of complications was related to inadequate digitalization, recent congestive heart failure, angina pectoris, poor cardiac function, pulmonary *emphysema, azotemia and obesity.*

Syphilitic Cardiovascular Disease

In asymptomatic cases operation is usually well tolerated. In the presence of angina pectoris or heart failure the surgical risk increases considerably.

THE CHOICE OF ANESTHESIA

The anesthetic agent administered by a skillful anesthetist is rarely a significant factor in surgical risk, either in the cardiac or non-cardiac patient.[8] However, the diseased heart is usually more sensitive to myocardial anoxia and therefore to deficient oxygen in the anesthetic mixture. This applies particularly in cases of advanced coronary atherosclerosis, aortic steno[illegible] *syphilitic coronary ostial stenosis* and those with Adams-Stokes syndrome. Sudden and severe reductions in arterial pressure are also particularly dangerous to these patient[illegible] diminished coronary reserve. In the above-*mentioned groups of cases* there is a tendency to sudden death and factors [illegible] coronary blood flow or myocardial oxygen[illegible]tion increase that tendency. The p[illegible]logic effects of anesthesia on the hea[illegible] been *reviewed* by Meek.[87]

The oft-stated rule that the ch[illegible] skilled anesthetist is more importa[illegible] type of anesthetic agent bears rep[illegible] corollary it may be said that in [illegible] *cardiac patients the anesthet*[illegible] the anesthetic with which he [illegible] familiarity and skill rather tha[illegible] preferable one with which h[illegible] experience.

During induction and the [illegible] thesia, emotional exciteme[illegible] ertion by the patient, hypo[illegible] significant changes in blood [illegible] ished coronary flow or incre[illegible] of the cardiac muscle *should* [illegible] liberal supply of oxygen is [illegible] less of the anesthetic. The [illegible] thetic must be made with re[illegible] problems of the surg[illegible] operation.

Local anesthesia or reg[illegible] caine or similar prepara[illegible] when possible for minor [illegible] rine is best avoided in all [illegible] is contraindicated in pa[illegible] artery disease. Barbitura[illegible] istered before the us[illegible] anesthesia appears inad[illegible] Pentothal sodium in 2 [illegible] may be given intrave[illegible] tions or for extraperi[illegible] are not very long and [illegible] great abdominal relax[illegible] per cent oxygen and [illegible] are important adj[illegible] thesia. Intravenou[illegible] combined with a [illegible] nitrous oxide and [illegible] tube to maintain [illegible]

both in children and adults for all transpleural operations and should be inserted when the patient is well anesthetized

The most reliable inhalation anesthetic for major operations in cardiac patients is *ether* because of maximal experience with this agent and because of the absence of serious disadvantages Ether is administered by means of the carbon dioxide absorption technique Nitrous oxide with at least 50 per cent oxygen may be used for induction A combination of cyclopropane with ether and oxygen may give a smoother induction with pleasanter awakening and less nausea or vomiting [6]

Cyclopropane without ether, is undesirable because of the risk of inducing serious cardiac arrhythmias especially in patients with coronary artery insufficiency [30] It is therefore permissible only for induction of anesthesia and then in combination with high concentrations of oxygen Induction of anesthesia with cyclopropane has been recommended for cardiac patients because of the smoothness and rapidity of induction and its prompt controllability [30] Nitrous oxide and ethylene have been regarded by some as undesirable in cardiac patients because they are not combined with sufficient oxygen when the concentration of these agents is high enough to produce adequate anesthesia But adequate oxygenation can be provided, and under such circumstances ethylene reinforced with small amounts of ether has been used successfully in rheumatic cardiac patients undergoing mitral commissurotomy Chloroform should not be used in cardiac patients because of direct toxic effect on the heart Epinephrine should not be administered during general anesthesia and especially with cyclopropane because of the danger of causing ventricular fibrillation and cardiac arrest

Spinal anesthesia is usually avoided in cardiac patients (except low spinal or caudal anesthesia in vaginal or rectal operations) because of the danger of a sharp reduction in diastolic pressure The contraindication applies particularly to patients with a high diastolic blood pressure However this objection may be overcome by the proper use of vasopressor drugs such as Neosynephrine and the concomitant administration of 100 per cent oxygen Pituitrin should not be used for its vasopressor effect because of its pronounced coronary constrictor action In some patients with congestive heart failure inhalation anesthesia may be entirely undesirable and the most satisfactory anesthesia may be obtained with low spinal or caudal anesthesia in combination with 100 per cent oxygen and a continuous intravenous drip of Pentothal sodium Low spinal anesthesia may be particularly satisfactory in heart failure, since it causes pooling of blood in the lower extremities and viscera and prevents further pulmonary congestion and edema Hypotension is avoided by a preceding injection of 1 per cent Neosynephrine, 5 to 15 mg (0 5 to 1 5 cc) intramuscularly or 2 mg (0 2 cc) in an intravenous drip

MANAGEMENT OF THE SURGICAL CARDIAC PATIENT

In general the same rules of good surgical practice apply to cardiac as to non cardiac patients Only special points referable to the cardiac patient are briefly considered in the following discussion

PREOPERATIVE MANAGEMENT

See also sections on the individual cardiac lesions which are treated surgically, especially pp 671, 672

Preoperative sedation is effected in infants by morphine in doses of 1 to 2 mg and in older children either by morphine or seconal combined with scopolamine In adults morphine and scopolamine (0 3 to 0 4 mg) or atropine are usually administered Every effort is made to avoid apprehension or excitement and to allay anxiety

The intravenous administration of sodium containing fluids including blood, plasma or amino acid infusions *should be avoided*, or if essential, must be conducted with special caution as to quantity and rate of infusion The advisability of giving packed red blood cells instead of whole blood should be considered when transfusion is indicated because of preoperative anemia or because of blood loss during the operation The patient's head and shoulders should be elevated during the infusion Frequent examinations of the chest determinations of vital capacity, circulation time and venous pressure, and questioning as to dyspnea and orthopnea may help to avoid pulmonary edema and right sided heart failure by early discontinuation of the infusion

If heart failure is present preoperatively it should be controlled by reasonable bed rest by

digitalization of the patient by restriction of sodium intake and if necessary by the administration of mercurial diuretics The method and speed of digitalization (Chapter 11) depend on the urgency of the operative procedure If the patient has been previously digitalized maintenance doses of digitalis should be continued preoperatively and thereafter Patients with atrial fibrillation and rapid ventricular rate should be given adequate amounts of digitalis to slow the ventricular rate to normal When heart failure is due in part to loss of blood or to anemia of other origin it may be most readily controlled by correction of the anemia Similarly the parenteral administration of thiamine chloride and the correction of a protein deficiency are sometimes essential measures in the preoperative control of heart failure

If possible therapy of heart failure including intelligent bed rest (with the patient s head elevated) should be maintained for at least two or three weeks after the heart failure is controlled before the operation is performed But an operation should not be deferred until heart failure is controlled if the heart failure is due chiefly to a condition which the operation is designed to correct e g a constrictive pericarditis or arteriovenous aneurysm If an operation is performed for a surgical emergency despite the presence of heart failure 0 25 mg of ouabain may be administered intravenously and repeated in a half hour and again in two to four hours if necessary provided that the patient has not received digitalis in the preceding two weeks The effectiveness of preoperative control of heart failure is indicated by the experience of Hamilton[49] who *reported 144 cases of overt* heart failure on admission in which a major surgical operation performed after satisfactory preoperative treatment was associated with a mortality of only 5 5 per cent

In patients with angina pectoris the frequent sublingual administration of nitroglycerin preoperatively may be beneficial

In patients who are to have an operation on the genitourinary tract as in patients having dental extraction 0 5 gm tetracycline (Achromycin) 500 000 units of aqueous penicillin 600 000 units of penicillin procaine and 1 gm of streptomycin should be given intramuscularly one half hour before the procedure because of the risk of bacterial endocarditis This should be repeated every 12 hours for two or three days postoperatively If there has been any history of bronchopulmonary disease bronchodilators should be given in addition to the antibiotics

Insulin must be given with extreme caution preoperatively to diabetic patients with coronary artery disease lest a resulting hypoglycemia induce a myocardial infarction Epinephrine pituitrin and ergot are drugs to be avoided preoperatively during or after the operative procedure

MANAGEMENT DURING OPERATION

The normal body temperature should be maintained Prolonged narcosis should be avoided and to this end the operation should be limited to the essential minimal procedures The special vulnerability of the cardiac patient enhances the importance of minimal handling of tissues skillful technique proper hemostasis and adherence to all other good surgical principles Loss of blood due to avoidable surgical trauma or improper hemostasis because of its deleterious anoxic effect on the diseased heart is especially inexcusable Such blood loss should be corrected promptly by the cautious transfusion of blood or of packed red blood cells If there is a history of or danger of left heart failure the operation should be conducted whenever possible with the patient s head and shoulders elevated

The occurrence of heart failure during operation may be indicated by acute pulmonary edema The patient should be placed in Fowler s position the anesthetic discontinued and oxygen administered in high concentration by mask under positive pressure of 5 to 10 mm Hg *Rotating tourniquets should* be applied to the extremities If these measures are ineffective morphine sulfate aminophylline intravenously and Cedilanid intravenously may be administered in succession at appropriate intervals (p 263) If the heart failure is due to an arrhythmia appropriate corrective measures should be instituted (infra)

Shock during operation (p 309) is treated according to the cause Blood replacement adequate oxygen supply and ventilation and the use of vasopressor drugs (p 502) may be indicated

Cardiac Arrhythmias During Operation

The relative frequency of cardiac arrhythmias during operation especially during

cardiac surgery,[14, illegible] and the importance of prompt diagnosis and treatment indicate the need for constant monitoring of the cardiac rate, rhythm and conduction by means of the oscilloscope and the use of a direct writing electrocardiogram for a permanent record. Electrocardiographic abnormalities were described in about 80 per cent of a series of 109 patients under anesthesia with a variety of anesthetic.[illegible] Eisaman et al.[illegible] observed arrhythmias in 62 per cent of 113 patients who received cyclopropane, chiefly multiple and multifocal ventricular premature beats. The intravenous administration of 1 per cent procaine was beneficial in 93 per cent of the cases, but this drug was avoided in cardiac arrest. On the other hand, arrhythmias, most commonly of atrial origin, were observed in only 9 per cent of 221 patients who had received Pentothal for induction and nitrous oxide and ether anesthesia. The arrhythmias during operation have been attributed to direct manipulation of the heart or adjacent structures, to reflex effects of the surgical procedure on the heart, to the induction or the depth of anesthesia, to hypoxia, hypercapnia, metabolic changes or hemorrhage.

In general, proper management of the arrhythmias should stress prevention and elimination of the cause. Whenever feasible, correction of all possible contributing causes of the arrhythmia should be carried out before the addition of cardiac drugs is undertaken. Cardiac arrest is discussed separately (infra).

Sinus tachycardia usually requires no treatment except to check that there is an optimal supply of oxygen and efficient ventilation. During ether anesthesia it may be an indication to diminish the depth of anesthesia or as some have recommended, to administer small amounts of cyclopropane. For severe tachycardia, occasionally neostigmine (1 mg intramuscularly) or Tensilon (edrophonium) (10 to 20 mg intravenously) may be given.

Sinus bradycardia may be due to vagal reflexes initiated by the anesthetic or the surgical procedure. If severe, it may be treated by the intravenous administration of atropine (0.4 to 1.0 mg). The patient should be well oxygenated and hyperventilated first and atropine injected only if severe bradycardia persists.

Supraventricular tachycardias which persist may be treated by the intravenous administration of neostigmine methylsulfate (0.5 to 1.0 mg). Procaine 1 per cent (100 mg) and procaine amide 10 per cent solution (100 to 500 mg) have also been used successfully.

Paroxysmal atrial flutter and fibrillation may be treated by Cedilanid, 4 cc (0.8 mg) intravenously, and this is repeated if necessary provided the patient has had no digitalis. Otherwise, procaine amide 100 to 500 mg may be given intravenously.

Ventricular premature beats, when very frequent, and *ventricular tachycardia* may be controlled by 100 to 500 mg of procaine amide administered intravenously. This should be given cautiously with electrocardiographic control, and vigilance for the possible development of hypotension or convulsions.

The appearance of severe *conduction disturbances* is an indication to withdraw the anesthetic and administer oxygen. Atropine may be administered.

Cardiac Arrest in Surgery

Incidence. Cardiac arrest denotes the sudden stoppage of the heart and circulation. It may be due to cardiac (ventricular) standstill or ventricular fibrillation. Its frequency in the course of surgery has been variously reported as 1 in 3673,[39] 1 in 2382[82] and 1 in 1200 cases.[89] But in cardiac surgery it was observed as often as once per 41 cases in one series.[39] It may occur during induction of anesthesia, during endotracheal intubation, during the course of an operation and in 14 per cent of 1200 cases of cardiac arrest reported in various countries it occurred after the patient had left the operating room.[89]

Etiology of Cardiac Arrest. *Myocardial anoxia or hypoxia* is the major and commonest cause of cardiac arrest.[81, 83, illegible, 179] This results usually from impairment of the airway or of the ventilatory exchange or from insufficient administration of oxygen. Other causative mechanisms include vagal reflexes,[81, 74] hypercapnia[89, illegible] and hyperkalemia,[79] excessive anesthesia or sensitivity to the anesthetic and direct manipulation of the heart and great vessels.[89] Pentothal sodium is especially suspect. Often multiple factors appear to be involved, but hypoxia and vagal reflexes are the ones which are almost always directly or indirectly concerned. In cardiac operations direct manipulation of the heart or torsion of contiguous structures may be contributory to

if not entirely responsible for cardiac arrest, but this is most likely to occur in the presence of myocardial hypoxia.

Prevention of Cardiac Arrest. The prevention of cardiac arrest is stressed.[49] Avoidance of anoxia is the primary means of preventing cardiac arrest and this depends chiefly on the anesthetist with due cooperation of the surgeon. Maintenance of an airway at all times, adequate oxygen concentration in the anesthetic mixture and avoidance of excessive depth of anesthesia are essential. The surgeon can minimize anoxia by careful hemostasis, prompt blood replacement if necessary, minimal traction on abdominal or thoracic viscera to prevent vagal reflexes and minimal manipulation and distortion of the heart and great vessels in cardiac surgery. The use of atropine or scopolamine in children and adults has been recommended to minimize vagal reflexes.[4, 41] Procaine and procaine amide have been administered intravenously by some surgeons to prevent ventricular fibrillation and procaine has been instilled into the pericardium or cardiac cavity before actual cardiac surgery. The prophylactic value of drugs is unproven.

Prompt Diagnosis of Cardiac Arrest. Early diagnosis of cardiac arrest is essential for successful treatment. Restoration of an effective heart beat must be accomplished within a maximum of three to five minutes because this is the usual maximum period of anoxia which the brain will tolerate before death or serious irreversible damage occurs. The early diagnosis of cardiac arrest depends primarily on the anesthetist who is making continuous observation of the patient's vital signs. Sudden absence of the pulse and blood pressure denotes cardiac arrest. This should be promptly announced and action taken without confirmation by prolonged auscultation, electrocardiography, etc. In thoracic and especially in cardiac operations, the diagnosis of cardiac arrest may be made by the surgeon or by the physician who is monitoring the cardiac action by an oscilloscope. The anesthetist, physician or nurse in attendance should continue to watch for the possibility of cardiac arrest even after the patient leaves the operating room until he reacts from the anesthetic.

Treatment of Cardiac Arrest. Successful treatment of cardiac arrest requires prompt recognition and previously organized preparation with a set plan of action and readily available equipment.[53, 55] The heart beat must be restored and respiration maintained, preferably with the aid of administered oxygen. A cardiac resuscitation kit should be available at critical locations. This should contain a scalpel and a few other dissecting instruments, a costotome, endotracheal tube, syringes and 4 inch long 22 gauge needles and solutions of 10 per cent calcium chloride, epinephrine 1:1000, 2 per cent procaine, procaine amide and sterile saline.[43, 53] A defibrillation apparatus should also be readily available.[35, 9, 46, 65, 77]

One may begin attempted resuscitation by striking a sharp blow over the precordium which is occasionally effective.[74] If cardiac arrest occurs in the course of an abdominal operation, a few seconds only may be used in an attempt to restore the heart beat by cardiac massage by way of the diaphragm. If the patient is out of the operating room and there is any delay in procuring a knife, a long needle introduced through the fourth left intercostal space may be used to prick the heart once.[22] If a knife is still unavailable, 0.5 mg. atropine sulfate, 2 to 4 cc. of 10 per cent calcium chloride[5] and 0.3 cc. of 1:1000 epinephrine may be injected intracardially. Three patients who suffered cardiac arrest during surgical procedures were resuscitated by the intravenous infusion of molar lactate solution.[7] But these drugs should not be employed if a thoracotomy and direct cardiac massage can be instituted within a few minutes.

An external electrical stimulator[17, 82, 83] (p. 394) has served successfully as a cardiac pacemaker in certain cases of cardiac standstill. Zoll and associates[84] reported 8 successful cases of cardiac resuscitation from unexpected arrest during surgery in 7 and pericardiocentesis in 1. Cardiac arrest was terminated in each case by means of the electric pacemaker without resorting to thoracotomy or cardiac massage. This apparatus is ineffective when cardiac arrest is due to ventricular fibrillation or when treatment is delayed. If the cardiac arrest is due to ventricular fibrillation, it may be terminated by externally applied electric countershock.[85] The 120-volt line current must be converted to a range of 0 to 720 volts by a special 6:1 isolation step-up transformer and a variable autotransformer. Usually 240 to 720 volts were required. The current was

applied for a fixed period of 0 15 second at the second intervals When ventricular standstill follows defibrillation, an external cardiac pacemaker is employed to stimulate the heart If the external pacemaker and the apparatus for application of external countershock are not immediately available or effective, a thoracotomy should be performed promptly

As soon as a knife is available an incision is made in the fourth or fifth intercostal space from the left border of the sternum to the axilla Sterile facilities should be used only if immediately available The costal cartilages above and below may be cut to improve exposure The pericardium is incised, the ribs spread and both hands introduced to compress the heart between them Cardiac compression should be continued at the rate of at least 60 to 80 per minute, although experiments suggest that rates up to 120 per minute are even more effective[11, 10] Cardiac massage should be continued for at least an hour since resuscitation has followed even after periods up to approximately two hours Sometimes cardiac massage is supplemented by placing the patient in the Trendelenburg position and blood is infused rapidly intravenously or intraarterially If cardiac massage is ineffective after a few minutes atropine, calcium chloride and epinephrine may be injected intracardially as indicated above but massage should then be continued To obtain more uniform cardiac compression and avoid the fatigue of prolonged manual massage, a set-up has been devised to obtain regular cardiac compression by rhythmic insufflation of oxygen into the pericardial cavity ("pneumo massage" of the heart)[7b]

While efforts are undertaken to restore the heart beat artificial respiration must be maintained The tongue should be pulled forward and a pharyngeal airway inserted Artificial respiration may be accomplished by mouth to mouth or mouth to-mask[33] breathing initially but the use of an anesthesia machine and face mask to deliver 100 per cent oxygen under pressure should be instituted as soon as possible As soon as an endotracheal tube is available this should be inserted and oxygen administered intratracheally

Treatment of Ventricular Fibrillation When thoracotomy is first performed, an effort should be made to distinguish ventricular fibrillation from standstill and the diagnosis should be confirmed by oscilloscopic or electrocardiographic examination In the presence of ventricular fibrillation, cardiac massage is undertaken as above until the defibrillator is available[55, 5, 9, 46, 65, 77]

Defibrillation is designed to restore the normal cardiac rhythm, after producing momentary standstill, by passage of an electric current through the heart[90, 4] A single shock, lasting 0 1 second may be effective If not, several shocks are repeated at intervals of 0 5 to 1 0 second Usually 110 to 130 volts at 1 5 to 2 5 amperes are administered, but recently voltages of 220 to 250 have been employed for large hearts For children, a variable resistance is inserted into the circuit For protection from electric shock, the surgeon should wear two pairs of gloves, manage the electrodes with the aid of wooden handles, stand on a wooden stool or similar non conductive platform and avoid contact with the operating table when the shock is applied Risk is diminished also by an isolation transformer in the circuit Successful defibrillation should be controlled by observing the cardiac rhythm with an oscilloscope or direct-writing electrocardiogram Resuscitation has been accomplished as long as 1 hour and 50 minutes after the onset of ventricular fibrillation[1] The physician undertaking cardiac resuscitation should be aware that serious myocardial tears[47] have been caused by rough massage and myocardial burns by excessive voltage of the defibrillating current

If no defibrillation is promptly available or if defibrillation appears unsuccessful, 5 cc of 2 per cent procaine or 1 to 3 cc (100 to 300 mg) of a 10 per cent solution of procaine amide may be introduced directly into the right atrium or ventricle The intravenous administration of molar sodium lactate may also be tried[7] (p 393)

Various educational programs have led to an increase in early diagnosis of cardiac arrest and probable improvement in the incidence of successful resuscitation Nevertheless, the mortality has been approximately 70 per cent[25] in large series of collected cases and 25 to 30 per cent in recent small series[65, 14]

POSTOPERATIVE CARE

Attention is directed again to the need for caution in the intravenous administration of blood plasma or sodium-containing fluid as discussed above (p *1106*) If fluids must be

given parenterally because of postoperative nausea 5 per cent glucose in distilled water should be administered instead of saline Postoperative distention may be controlled by the inhalation of 100 per cent oxygen by gastric aspiration with a Levin tube and by control of any postoperative infection but pituitrin should not be given

If heart failure develops the appropriate measures mentioned under preoperative care should be instituted The excessive parenteral administration of fluids excessive blood loss during operation and infection are among the common causes of postoperative heart failure in cardiac patients The particular danger of infection for cardiac patients demands prompt and adequate administration of antibiotics if there is any doubt as to its presence

The special frequency of phlebothrombosis and pulmonary embolism among patients with heart disease suggests the importance of using anticoagulants postoperatively as well as other prophylactic measures These have been discussed in detail (p 576)

Cardiac arrhythmias following operation usually subside spontaneously in a few hours or days They may be controlled if necessary by the administration of appropriate drugs usually digitalis quinidine or both

DIRECT VISION CARDIAC SURGERY

Cardiac surgery by direct vision has been accomplished by the aid of (1) cross-circulation techniques (2) hypothermia and (3) mechanical techniques for by passing the heart Lillehei[62] reported successful curative open cardiotomies performed under direct vision on 101 of 138 patients Of these 49 patients with atrial septal defects were operated on under hypothermia The others with atrioventricular defects ventricular septal defects pulmonary stenosis and tetralogy of Fallot were operated on with the aid of cross circulation in 45 instances a reservoir in 5 a biologic oxygenator in 12 and an artificial mechanical oxygenator in 27

CROSS CIRCULATION TECHNIQUES

Direct vision surgery has been made possible by means of controlled cross circulation using a living human donor or by means of continuous perfusion from an arterial reservoir[63 64] These techniques involving venous inflow occlusion (of the venae cavae) for 5 to 40 minutes have been made possible by the use of the azygos vein or low flow concept[3] It was noted that dogs survived long periods of vena caval occlusion without sequelae if only the blood flow from their azygos veins amounting to less than 10 per cent of the cardiac output was permitted to enter the heart Accordingly during the period of cardiac and pulmonary by pass perfusion of the patient can be accomplished at rates of flow which are only one eighth to one fourth of the resting cardiac output without cerebral renal hepatic or other serious organ disturbance With these low rates of flow there has been a relatively low coronary sinus blood loss and great improvement in cardiac visibility in contrast with the conditions associated with large perfusion flows

A suitable donor is carefully chosen with respect to previous health and compatibility of blood with that of the patient Donor and patient are given a single intravenous dose of heparin (0 75 mg per pound of body weight) and a similar amount of protamine may be given to the patient at the conclusion of the intracardiac operation Both donor and patient are anesthetized the former with Pentothal curare the patient with combinations of nitrous oxide or cyclopropane for induction and Pentothal-curare for maintenance The patient s body temperature is carefully maintained at normal levels

Arterial blood from the donor is supplied to the patient by way of a cannula inserted through the superficial femoral artery with its tip lying in the abdominal aorta Venous blood returns from the patient to the donor by way of a cannula threaded into the saphenous vein with its tip lying in the iliac vein or inferior vena cava Tapes are placed about the venae cavae to obtain inflow stasis during the actual intracardiac procedure A tape with Rumel tourniquet attached is placed around the ascending aorta Thereby the root of the aorta is occluded briefly when necessary to obtain a bloodless field and then released momentarily to restore the coronary flow thus alternating until the procedure is completed A pump assembly controls the reciprocal exchange of blood between patient and donor A venous reservoir serves to maintain a free flow of blood and as an effective air bubble trap The donor does not lose blood during the procedure but the patient s blood loss

from the operative wound and from the interior of the heart are replaced during the procedure by equal volumes of citrated bank blood introduced through a cannula in the patient's saphenous vein

A related technique of cross circulation involves a similar perfusion set-up, but instead of the human donor, a reservoir of arterial blood collected from donors and a reservoir to collect the venous blood returning from the patient are used These reservoirs are standard siliconized blood collection bottles from which the air has been exhausted Arterialized blood is obtained by applying heat to the arms of the donors before performing phlebotomy Warden et al [58a] reported the successful repair of a high interventricular septal defect in an infant by means of this method

Results

Lillehei and associates[61] reported the use of cross circulation in intracardiac operations, by direct vision in 30 patients with a variety of congenital lesions including interventricular septal defects tetralogy of Fallot, atrioventricularis communis and isolated infundibular stenosis Suture closure of the ventricular defect with resection of the infundibular stenosis was performed in the tetralogy of Fallot with survival of 6 of 10 patients In one case of isolated infundibular stenosis the infundibular pulmonic muscle was resected and the preoperative right ventricular pressure of 136 mm Hg was reduced four months postoperatively to normal (25/0 mm Hg)

No donor mortality resulted in 39 operations and only one serious but temporary complication, before the technique was improved Ventricular fibrillation and conduction defects have not been a problem in the operated patients, presumably because of maintenance of normal body temperature and adequate myocardial oxygenation during inflow stasis During the latter the myocardium is relieved of its pumping action and requires only a fraction of the normal coronary flow No air embolism, hemolysis or postoperative hemorrhage has been reported

This technique is one of the most dramatic recent advances in cardiac surgery Nevertheless, possible risk to the healthy donor represents a theoretical hazard which will lead to hesitancy in adopting the procedure The amount of blood needed for young children is sufficiently small to permit the substitution of a reservoir of arterialized blood and a collection reservoir for venous blood, to replace the living donor *It is probable that* a mechanical heart lung by pass will ultimately serve in place of the human donor cross circulation technique (infra)

HYPOTHERMIA

The induction of hypothermia has also been used to permit cardiac surgery under direct visual control with a relatively bloodless field [80, 85, 31, 8, 3, 11, 29, 75] The oxygen requirement of the body is substantially reduced by general body hypothermia, permitting the surgeon to interrupt the circulation for a longer period of time than at normal body temperature The circulation through the heart is interrupted by clamping the superior and inferior venae cavae and azygos veins Such interruption may be safely maintained at normal body temperature for 2 to 3 minutes or slightly longer But at 28° C (83° F) the circulation may be thus interrupted safely for 15 to 20 minutes, which is adequate for the correction of certain cardiac lesions under direct vision with a relatively dry field Operations under hypothermia are usually conducted at a body temperature of 30 to 31° C (86° to 88° F) or slightly higher or lower On the other hand hypothermia is associated with the risk of inducing ventricular fibrillation, cardiac arrest and cardiac failure Ventricular fibrillation is particularly likely to occur when the body temperature is reduced below 26° Hyperthermia is better tolerated by infants and very young children than by older children and adults There is experimental evidence that ventricular fibrillation may be prevented by procaine infiltration of the sinoatrial node,[30] by coronary artery perfusion with neostigmine solution,[71] and by the use of a mixture of 5 per cent carbon dioxide and 95 per cent oxygen in artificial respiration The cardiac rhythm should be controlled throughout hypothermia by electrocardiography, and a defibrillator should be available

Various techniques have been employed to induce hypothermia Preanesthetic medication is first administered, e g Demerol and scopolamine and succinyl choline or d tubocurarine to prevent shivering The combination of phenergan Thorazine and Demerol has also been used [57] Anesthesia is induced by cyclopropane or small doses of Pentothal and maintained by ether and oxygen until

hypothermia is effected Positive pressure respiration is administered with sufficient hyperventilation to induce mild respiratory alkalosis

Infants and children have been cooled by placing them in a cold water bath cooled by ice cubes to a temperature of 6° C Adults have been cooled by wrapping them in refrigerated blankets through which a pump circulates refrigerant fluids while a rectal thermocouple records the rectal temperature Some surgeons have preferred to induce hypothermia by cooling the blood itself[73, 13] Venous blood drawn out through a catheter inserted in the superior vena cava by way of the external jugular vein is conducted through a cooling coil—a plastic tubing immersed in a refrigerant—and returned to the body by way of the femoral vein Or the blood can be cooled after opening the chest and withdrawing blood through a cannula inserted into the superior vena cava through the right atrial appendage and returning it to the inferior vena cava through another catheter through the right atrial appendage Hypothermia has also been induced with the aid of brain cooling by irrigation of the carotid blood[42]

Cooling to 30 C usually requires 20 to 30 minutes in children But the time may vary from 10 minutes for an 8 lb baby to one or two hours for an adult The patient is rewarmed to normal body temperature at the conclusion of the operation by placing him in a bed with warm water bottles or in a warm water bath or by means of a diathermy device Whatever method is employed final warming is completed by placing the patient in a bed with warm blankets

Hypothermia combined with inflow circulatory occlusion has been successfully employed in cardiac surgery for interatrial septal defects of the secundum type for total anomalous venous occlusion transarterial correction of pulmonary stenosis and in the resection and homologous graft replacement of the thoracic aorta[4] It has also been used in closed heart surgery in which circulatory occlusion is unnecessary but in which the lower metabolic needs associated with hypothermia permit better tissue oxygenation especially in poor risk cases or when cyanosis is present e g tetralogy of Fallot tricuspid atresia

PUMP-OXYGENATORS (ARTIFICIAL HEART MECHANICAL HEART)

Ultimately the performance of cardiac surgery under direct vision without haste will be performed with the aid of some form of mechanical pump or pump-oxygenator which diverts the circulation from the heart[■, 34, ■, 38, 44, 37, 41] Many such devices are now available Some pumps have served to bypass only the right side of the heart or only the left side but a complete cardiac bypass necessitates also a mechanical oxygenator to perform the function of the lungs The patient s lungs may be cannulated and employed as the oxygenator in combination with mechanical pumps Biologic oxygenators such as an autologous or homologous pulmonary lobe have also been employed together with a mechanical pump[13a]

The problems involved in the use of a mechanical pump oxygenator include not only the construction of a suitable type of pump which can be cleaned and autoclaved and an efficient oxygenator but also the avoidance of clotting hemolysis of erythrocytes and infection[31] In addition all open cardiac operations are beset with the danger of air embolism Clotting has been controlled by coating the apparatus with silicone and by the use of intravenous heparin but the latter has been responsible for annoying oozing of blood during the operative procedure Hemolysis has been minimized by improved pumps designed to reduce damage to erythrocytes

Mechanical oxygenators have been constructed to expose successive thin films of blood to an atmosphere of oxygen[42] The spinning disk oxygenator of Bjork[10] consisted of a series of disks which were mounted on and rotated about a common horizontal shaft dipping into a pool of blood and forming a changing film of blood at the periphery of the disk The spinning screen oxygenator of Dennis[5] consisted of a series of rotating wire mesh disks near the centers of which blood was distributed, it was then spread into thin films over the entire disk by gravity and centrifugation These oxygenated blood by dispersing it in oxygen Other oxygenators such as the small bubble gas dispersion oxygenators of Clark et al[■, 44] and the large bubble oxygenator of Thomas and Beaudoin[47] disperse bubbles of oxygen into blood The

residual gas was then separated by defoaming facilities or by buoyancy In the foam oxygenator of Gimbel and Engelberg[38] the blood was oxygenated as it cascaded down a densely packed column of foam Two valve less rotary pumps were used, a venous pump to supply the oxygenator with blood and an arterial pump to deliver oxygenated blood to the patient The speed of the pumps was controlled electrically by signals from manometers which measure the volume of blood in the oxygenator and the pressure in the arterial and venous parts of the circuit

An apparatus to by pass the right side of the heart, and its use in animals, has been described by various investigators Dodrill[27] reported its successful use to perform a pulmonary valvuloplasty in a 16 year old boy with isolated pulmonic stenosis and intact septa A by pass of the left side of the heart especially useful for the surgical treatment of mitral and aortic valvular lesions has been utilized experimentally and in humans by Dodrill et al[28, 7] Blood was withdrawn from the pulmonary veins or left atrium passed through the mechanical pump and returned to the aorta by retrograde passage through the left subclavian artery Thus the left atrium, mitral valve area and left ventricle are full of blood and may be operated under direct vision provided there is no aortic regurgitation Dodrill[27] has reported the use of a mechanical by pass of both sides of the heart while the patient's lungs continued to function in an 18 year old girl operated on for pulmonic stenosis with possible ventricular septal defect

Kirklin et al[84] reported the performance of precise unhurried intracardiac surgery with a mechanical pump oxygenator system of the Gibbon type[51] in 8 patients with very severe congenital heart disease The period of cardiotomy varied from 20 to 73 minutes In 4 of the patients there was a ventricular septal defect, in 2 a persistent common atrioventricular canal and in one each an atrial septal defect and the tetralogy of Fallot Increased pulmonary vascularity, severe pulmonary hypertension and right ventricular hypertrophy were present in 7 of the patients Four of the 8 survived and are well In a subsequent publication DuShane et al[30a] reported the repair of ventricular septal defects in 20 children, under direct vision with the aid of this mechanical pump oxygenator (see p 1113)

Cannulae within the superior and inferior venae cavae diverted the patient s venous blood to the apparatus The output of venous blood from patient to machine was kept constant by gentle controlled suction Arterialized blood from the apparatus was returned to the patient through a filter to a cannula in the left subclavian or innominate artery The oxygenator consisted of 14 wire mesh screens, 12 by 18 inches each enclosed in a Lucite case Flows of 100 to 200 cc per kilogram per minute were obtained The oxygen saturation was 100 per cent in the blood returning to the patient 60 to 85 per cent in the venous blood Hemolysis was minimal Heparin was administered pre operatively to diminish the coagulability of the blood and protamine was administered after the operation to restore normal coagulability

Lillehei et al[6] have reported the performance of intracardiac surgery under direct vision in 36 patients whose hearts and lungs were totally by passed for periods of up to 50 minutes, by using a simple pump-oxygenator system The pumps employed were those used in their cross circulation technique The oxygenator, of the large bubble dispersion type, represents an effective ingenious improvement over previous devices It is simple in construction, without moving parts, and is assembled from commercially available plastic (pure polyvinyl) tubing and can be sterilized by autoclaving Since the cost of the oxygenator is only a few dollars Lillehei et al[6] have preferred to dispose of it after each clinical use rather than to clean and use it again

Oxygenation was accomplished by direct introduction of humidified, 100 per cent oxygen in the form of large bubbles which enter near the base of a vertical plastic mixing tube through multiple circumferential No 2? intravenous needles with their hubs cut off The needles are inserted circumferentially through an ordinary laboratory rubber stopper As the bubbles rise in the column of venous blood which also enters and circulates in the vertical mixing tube the blood-oxygen contact at the surface offers the large surface area necessary for efficient oxygen uptake and elimination of carbon dioxide, without need

of a foreign substance (such as disks or meshes) to produce blood films Momentary contact with a potent non toxic silicone anti foam substance sprayed or painted on the distal (U shaped) portion of the walls of the mixing tube and a smaller connecting tube dissipates the bubbles Because of their large size any remaining bubbles rapidly rise to the surface and are eliminated carrying off the carbon dioxide The oxygenated blood de scends by gravity in a spiral plastic settling tube and enters the central collecting reser voir an ordinary Kelly flask lined with a polyethylene bag from which it is perfused through the patient after passing through standard blood filters The flow of oxygenated blood from the pump-oxygenator system dur ing the interval of total heart lung by pass varied from 172 cc per minute to 600 per minute The patient s plasma hemoglobin in blood drawn immediately after perfu sion was not excessive varying between 17 and 45 mg per cent

Twenty five of the 36 patients had curative surgery for ventricular septal defects as sociated with pulmonary hypertension with 7 deaths Of 6 patients with the tetralogy of Fallot who underwent corrective surgery 2 died The other 5 survived intracardiac opera tions for atrial septal defect atrioventricularis communis or complete transposition of the great vessels In the last 10 operations all performed on seriously ill patients with ven tricular septal defects or tetralogy of Fallot there were 2 deaths

EXTERNAL SHUNTS

External plastic shunts have been used to by pass the circulation around the aortic and pulmonic valves and the proximal great vessels[16 24] Cross et al[24] showed that such shunts could carry the entire cardiac output for periods of 30 to 80 minutes in 26 dogs thus obviating the need for hypothermia or mechanical pump oxygenators

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Chapter 49

INSURANCE AND MEDICOLEGAL PROBLEMS IN CARDIAC DISEASE

The facts of cardiology are no different when applied to insurance and medicolegal problems from those of ordinary clinical practice as described in previous chapters of this book. Unfortunately this is not always apparent in the statements of physicians engaged in forensic medicine or in the decisions of judicial referees or courts. There is great need for reorientation of physicians, lawyers, judges and legislators with respect to the medicolegal aspects of cardiology in order to direct their opinions and judgments into greater harmony with the available body of scientific fact. This applies with particular emphasis to the physician who should not compromise with or distort established facts in order to abet legal interpretations based on erroneous interpretations of medical concepts. Neither should his scientific opinions be prejudiced by economic, emotional, sociologic or political bias.

The following pages include brief mention or discussion of some of the more frequent cardiac problems encountered in insurance and forensic medicine. The cardiac facts which should enable the physician to cope with these problems have already been presented in previous chapters.

CARDIOVASCULAR EXAMINATION AND ACCEPTANCE FOR INSURANCE

The medical examiner for an insurance company or for an industrial plant is often handicapped in making an evaluation of the cardiac status of an insurance applicant. An accurate or complete history is often unobtainable and facilities for roentgen ray and electrocardiographic examination and sometimes even for complete physical examination are often unavailable, especially when the applicant is examined at his place of employment. Thus moderate grades of cardiac enlargement are undiscovered. In the absence of electrocardiograms severe coronary disease may be overlooked, for the physical examination may be negative and a history of clinical symptoms may be concealed by the applicant. If there are no facilities for examining the subject in the left lateral recumbent position, an apical presystolic murmur of mitral stenosis may not be discovered.

On the other hand, a private physician may tell his patient after careful examination, that he is entirely normal only to have his application for life insurance rejected because of a cardiovascular abnormality. Or else the applicant is first rejected because of cardiovascular disease but subsequent examination by his private physician fails to disclose a significant abnormality. In such instances the discrepancy between private and insurance examinations is due to the wide range of normal values and differences in interpretation of borderline findings.

Among the commoner borderline findings responsible for insurance rejection are a systolic murmur, a slightly elevated blood pressure and a rapid pulse rate. The problem of differentiating the insignificant functional from the organic systolic murmur has been discussed (p. 617). The applicant's personal physician, with a complete and reliable history and every needed diagnostic aid, may reasonably conclude that a given systolic murmur is functional and not due to cardiac disease. Without these advantages of accurate history and complete diagnostic facilities the insurance examiner may be inclined to interpret the murmur as being more significant. Not infrequently individuals with an inconsequential systolic murmur are rejected for life insurance because of the greater than standard risk associated with any large *group*

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CARDIOVASCULAR EXAMINATION AND ACCEPTANCE FOR INSURANCE

The medical examiner for an insurance company or for an industrial plant is often handicapped in making an evaluation of the cardiac status of an insurance applicant. An accurate or complete history is often unobtainable, and facilities for roentgen ray and electrocardiographic examination and sometimes even for complete physical examination are often unavailable, especially when the applicant is examined at his place of employment. Thus moderate grades of cardiac enlargement are undiscovered. In the absence of electrocardiograms severe coronary disease may be overlooked, for the physical examination may be negative and a history of clinical symptoms may be concealed by the applicant. If there are no facilities for examining the subject in the left lateral recumbent position, an apical presystolic murmur of mitral stenosis may not be discovered.

On the other hand, a private physician may tell his patient after careful examination, that he is entirely normal only to have his application for life insurance rejected because of a cardiovascular abnormality. Or else the applicant is first rejected because of cardiovascular disease but subsequent examination by his private physician fails to disclose a significant abnormality. In such instances the discrepancy between private and insurance examinations is due to the wide range of normal values and differences in interpretation of borderline findings.

Among the commoner borderline findings responsible for insurance rejection are a systolic murmur, a slightly elevated blood pressure and a rapid pulse rate. The problem of differentiating the insignificant functional from the organic systolic murmur has been discussed (p. 647). The applicant's personal physician, with a complete and reliable history and every needed diagnostic aid, may reasonably conclude that a given systolic murmur is functional and not due to cardiac disease. Without these advantages of accurate history and complete diagnostic facilities the insurance examiner may be inclined to interpret the murmur as being more significant. Not infrequently individuals with an inconsequential systolic murmur are rejected for life insurance because of the greater than standard risk associated with any large group

of persons with a systolic murmur Reversal of this judgment may follow appeal to and more detailed reexamination by physicians at the home office of the company

The range of normal blood pressure is not sharply defined If 140 and 90 mm Hg are chosen as the upper limits of normal systolic and diastolic pressures respectively, many normal individuals may be refused insurance or compelled to pay increased rates On the other hand more liberal interpretations of normal would result in the insurance of many individuals with a higher average death rate than that of more rigidly normal controls Even when a definite elevation of blood pressure is found to be transient, the applicant may be considered less than a standard risk from the actuarial viewpoint For there is evidence that persons with transient hypertension are much more prone to the later occurrence of sustained hypertension and cardiorenal disease than normal controls A tachycardia, even if transient, may likewise be associated with increased life insurance risk, since individuals with transient tachycardia are also found to develop sustained hypertension and cardiorenal disease more often than normal controls

Other borderline cardiac findings sometimes responsible for increased insurance rates or rejection of individuals whose hearts are probably normal include premature beats, pronounced bradycardia, and T wave abnormalities in the electrocardiogram due to rotation or other positional changes of the heart It is, therefore, often helpful and desirable for the applicant's physician and the insurance medical examiner to cooperate in determining as accurately as possible the significance of these minor deviations in the particular individual in question It is unfair to apply the less favorable prognosis of a heterogeneous group with a given cardiac finding to every individual with that finding when it may be possible to demonstrate its insignificance in a given instance

WORKMEN S COMPENSATION AND HEART DISEASE

Most of the medicolegal problems involving cardiac disease arise in connection with claims for workmen's compensation based on cardiac disability or death attributed to an unusual strain or injury suffered unexpectedly in the course of the claimant's employment

Preexisting Heart Disease

When direct penetrating or non penetrating injuries affect the precordial region, cardiac disability may occur whether the heart was previously well or diseased On the other hand, there is virtually no substantial evidence that strenuous exertion can damage the normal heart Yet most of the claims for compensation are based on cardiac disability attributed not to direct trauma but to unusual exertion, lifting or other physical strain In such cases it follows from the above that a causal relation between the strain and the cardiac disability appears more probable in the presence of preexisting cardiac disease than in its absence

Since cardiac disability is the usual natural consequence of organic cardiac disease, it would appear illogical, in the presence of preexisting disease, to attribute such disability to some extraneous exertion with any high degree of probability But according to most compensation laws preexisting cardiac disease is no bar to compensation if the actual disability or death is deemed to arise from some unusual and extraordinary exertion connected with an individual s employment This exertion or strain is interpreted as the determining cause of disability if it aggravates or accelerates the course of the underlying disease and thereby leads to cardiac disability or a fatal end sooner than would otherwise have occurred Furthermore most workmen's compensation decisions have failed to apportion responsibility between the underlying cardiac disease and the strain When cardiac disability was held to result from such strain, the latter was deemed totally responsible

From the medical, as contrasted with the legal, viewpoint the physician must attempt to assess the probable natural course of the underlying cardiac disease on the basis both of known data concerning the disease and of its history in the individual in question Then he must estimate whether the underlying disease was unusually and unexpectedly aggravated or accelerated, and if so, whether the alleged strain was the probable cause of this unfavorable acceleration This decision is particularly difficult because coronary thrombosis, serious arrhythmia and heart failure often appear suddenly and unexpectedly in the natural course of the preexisting disease without unusual exertion or other apparent cause Furthermore medical

testimony in workmen's compensation cases is often not supported by any strong significant evidence relating the onset of symptoms to some particular incident during employment. Certain diseases such as coronary atherosclerosis with angina pectoris, coronary occlusion, calcific aortic stenosis and syphilitic aortitis with coronary ostial stenosis are likely to terminate in sudden unexpected death independently of any physical strain. There is rarely a scientific medical basis for deciding whether sudden death in the presence of these diseases was precipitated by physical strain arising in the course of employment or was a natural phenomenon of the disease. When an individual suffers from preexistent calcific aortic stenosis or heart block he may experience attacks of dizziness or syncope which may be fatal. In the course of such an attack he may suffer an injury which is the result of the fatal cardiac episode rather than the cause.

The Relation of Strain to Cardiac Disability

In actual medicolegal practice the physician is queried much less about the pathology, symptomatology or natural course of the preexisting disease than about the role of some physical strain or "accident" in producing angina pectoris, coronary occlusion, myocardial infarction, a disabling arrhythmia, heart failure or unexpected death. Unfortunately the answers to this latter question are rarely strongly buttressed by scientific factual data. They are often determined by personal estimates of probability and reasonableness with emphasis on a post hoc propter hoc type of logic. Frequently the physician is called upon to give his answer in a "yes" or "no" form to an hypothetical question when neither the question nor the answer fully encompasses a just consideration of all the facts and all the gaps in our medical knowledge.

The physician must first determine the presence and degree of cardiac disability following the alleged injury and whether this differs from any disability present prior to the injury. The most frequent manifestations attributed to cardiac strain include more or less immediate cardiac pain, acute dyspnea, faintness, dizziness, syncope or collapse, cold sweat, palpitation and cardiac irregularity followed by subsequent recurrent angina pectoris or evidence of myocardial infarction or congestive heart failure. Confirmation of a change in the cardiac status may be supplied by serial electrocardiograms following the injury, especially if they can be compared with electrocardiograms taken previous to it.

The physician must then determine whether the given strain was adequate to produce the cardiac disturbance and whether, considering the complete history and findings, the strain in all probability did cause the disability. Various criteria have been proposed as a basis for relating cardiac disability to a physical strain, among which the following may be mentioned: (1) the physical exertion is of unusual severity and more intense or involving greater strain than that previously regularly performed by the affected person; (2) the onset of symptoms of cardiac strain is relatively sudden and follows immediately or very soon after the alleged causative exertion; (3) physical exertions perviously executed without difficulty cannot be undertaken or endured. It must be apparent that since preexistent heart disease is usually present, satisfaction of these criteria does not exclude the possibility of coincidence rather than causal relationship.

According to most workmen's compensation decisions involving the heart, compensation is awarded for an "accidental injury" sustained in the course of and arising out of an individual's employment which causes disability of the heart, aggravates or accelerates preexisting disease or causes sudden death. An accident is interpreted as an unforeseen and unexpected occurrence and includes extraordinary physical strain which is not usual to the employment. In addition to lifting, straining and other physical exertions, accidental injuries causing coronary insufficiency or heart failure have been ascribed to "nervous shock," exposure to toxic gases including carbon monoxide and sulfur dioxide, infections sustained in the course of employment, electric shock and even to an injection of tetanus for a wound received in the course of work. The development of heart failure in association with lower nephron nephrosis due to carbon tetrachloride exposure may be an additional basis for workmen's compensation claims.

Degree of Disability: Total and Permanent Disability

Having stated that in his opinion there is cardiac disability due to some accidental extraordinary exertion, the physician may be

asked to assess the degree of disability sustained and to state whether this disability is temporary or permanent From the medical viewpoint it should be emphasized that neither the existence of clinical manifestations of coronary sclerosis including those of myocardial infarction, nor the presence of electrocardiographic abnormalities nor even the mild grades of cardiac failure denotes total and permanent disability A substantial percentage of individuals return to gainful employment following recovery from an acute myocardial infarction Because of differences in individual response to disease the evaluation of partial or total disability should be made individually in each case and not on the basis of the general etiologic or pathologic diagnosis Evaluation of "permanent" disability is often equally difficult because of the well known hazard of prognostication The word 'permanent" must be used with the reservation that it may be subject to revision after continued observation

Workmen s compensation decisions interpret 'permanent and "total disability" very liberally It is unnecessary for the claimant to be entirely incapacitated or inert It suffices to prove that his disability prevents him from performing in his usual manner all the essential duties of his occupation which his age, training, experience and physical condition would permit if not for the accidentally induced cardiac infirmity Thus disability is interpreted in terms of the employe s particular occupation, business or profession and not in terms of other forms of employment or of general physical capacity

Coronary Heart Disease

Most claims of compensation for cardiac disability allege the production of angina pectoris coronary thrombosis or myocardial infarction by unusual physical strain or less often by toxic agents infections or emotional shock A causal relationship between penetrating or non penetrating chest trauma and coronary and myocardial injury is well established by scientific medical evidence (Chapter 44) But the evidence linking physical strain to coronary thrombosis is tenuous

Our present medical knowledge indicates clearly that coronary thrombosis and myocardial infarction almost always occur on the basis of preexisting severe coronary atherosclerosis, whether or not there was manifest clinical evidence The thrombosis or occlusion is a common inherent incident in the natural life history of the progressive coronary atherosclerotic process, and in 95 per cent or more of cases it appears without causal relation to any unusual physical strain It occurs at least as often among sedentary as among manual workers and at rest or sleep as often as during activity

In occasional instances coronary occlusion is preceded by such an intense and extraordinary physical strain the previous history is so apparently free from cardiac abnormality, and the onset of cardiac manifestations occurs so promptly after the strain that it is difficult to avoid the conclusion that the strain actually produced or precipitated the coronary occlusion or myocardial infarction Since intimal hemorrhage in an atherosclerotic plaque may lead to occlusion (p 500), it has been hypothesized that an unusual physical strain may raise the blood pressure and cause an intimal hemorrhage It has also been suggested that a severe physical strain, by increasing the work of the heart and its need for blood, intensifies a preexisting relative myocardial ischemia to the point of necrosis (infarction)

The difficulty of relating a coronary occlusion and myocardial infarction to a physical strain increases when distinctive clinical manifestations appear only after an interval of many hours, days or weeks Yet there is evidence that such an interval may actually elapse between the onset and the full development of coronary occlusion and cardiac infarction Occasionally a transient minor or severe clinical symptom occurring immediately after an unusual exertion appears to be followed by complete recovery Only days or weeks later is the evidence of recent myocardial infarction discovered and the claim is made that the initial immediate symptom represented the onset of a coronary occlusion due to physical strain This type of case stresses the value of routine and repeated electrocardiograms promptly after any unusual effort which is suspected of having caused cardiac injury

Sometimes a traumatic injury is followed by infection and prolonged invalidism and culminated by a disabling or fatal coronary occlusion Even in such cases courts or

referees have affirmed a causal relation between the infection and physical and mental suffering and the coronary occlusion even though much more hypothesis than medical fact is adduced to support such an interpretation Rarely a myocardial infarct has been attributed to a coronary embolism arising in a venous thrombus at the site of injury of an extremity In the absence of cardiac septal defects this could not occur and even in their presence there is no evidence that coronary embolism and cardiac infarction do occur In this connection the section on fat embolism should also be reviewed (p 966)

Valvular Disease, Arrhythmias and Heart Failure

Penetrating and non penetrating injuries of the chest may cause myocardial contusion pericarditis or hemopericardium arrhythmias rupture of valves or heart wall and heart failure or rapid death In some instances of non penetrating chest trauma it is difficult to prove the actual occurrence of cardiac injury, but this difficulty can usually be avoided if careful physical roentgenologic and electrocardiographic examinations are made promptly and repeatedly after the trauma

An unusual physical strain may rarely rupture the chordae tendineae or cusps of a diseased valve, but extremely rarely if ever is a normal cusp so ruptured Since rupture of the chordae may occur spontaneously the extraordinary nature of the alleged strain must be carefully evaluated before it is credited as the causative factor

Bacterial Endocarditis

This has been attributed to trauma and infection occurring in the course of employment A decision as to causal relationship may be aided by bacteriologic study of the blood and if possible, by comparison of the organism obtained on blood culture with that of the organism responsible for the infection in the traumatized area

Cardiac Neurosis

Not infrequently the persistence of symptoms such as precordial pain dyspnea and fatigability following a chest trauma or an unusual physical strain are due to a cardiac neurosis and not to organic damage to the heart In this as in other forms of traumatic neurosis early settlement of litigation is often an effective prophylactic against prolonged invalidism

LIFE HEALTH AND ACCIDENT INSURANCE

Total and Permanent Disability

The difficulties of evaluating the presence of total and permanent disability in connection with benefits provided under life health or accident insurance policies are similar to those connected with workmen s compensation claims and have already been discussed In recent years life insurance claims of total and permanent disability were particularly frequent when an individual suffered from angina pectoris or coronary thrombosis The economic depression and unemployment undoubtedly increased the pressure to make such claims In some instances fraudulent claims were supported by electrocardiographic abnormalities secretly induced by digitalis Fortunately this problem is becoming outdated as life insurance policies with benefit provisions for total and permanent disability have been granted rarely in recent years

Accidental Death and Double Indemnity

One of the problems arising in association with life insurance policies is the provision for double indemnity or payment of twice the face value of the policy if the insured dies of an accident A similar problem occurs in connection with accident policies which provide the payment of a lump sum in instance[illegible] accidental death We are particularly c[illegible]cerned with those instances in which [illegible] accident is claimed to have caused a card[illegible] death But in contrast with claims of wo[illegible]men s compensation it is necessary to pr[illegible] that death occurred exclusively as a result [illegible] an accident independent of any preexist[illegible] disease Under such circumstances it may [illegible] relatively easy to demonstrate a cau[illegible] relationship between death and penetrat[illegible] chest wounds severe non penetrating ches[illegible] trauma and occasional toxic agents if the onset of symptoms is immediate and death occurs promptly or as an end result of an uninterrupted progression of the immediate symptoms On the other hand it seems impossible to justify a cardiac fatality, on the basis of an extraordinary physical strain, if the heart and coronary arteries are presumed to have been previously free from disease In practice however the problem is made difficult by the claim that any preexisting disease was inactive or arrested and that the fatal cardiac disturbance must [illegible] ed en

tirely to the accidental strain which activated the "arrested" disease The physician who is required to give an opinion should adhere as far as possible to a presentation of what is known medically without becoming involved in inconsistent legalistic definitions or interpretations From the medical viewpoint, any opinion as to possible relationship between a given stimulus and a cardiac fatality should be the same whether given before a workmen s compensation referee or in a court trying an insurance claim for accidental death

PERSONAL LITIGATION

The medical problem in personal litigation (tort law) arising out of cardiac injuries is identical with that described under the above headings The physician may be askec opinion as to the presence of cardiac the degree and duration of disabili whether a given alleged injury in al ability was responsible for the disturbance In practice the prob personal litigation differs from that o men's compensation in that liability defendant must be demonstrated basis of intentional or negligent expo the claimant to the injury Furthermoi compensation as the claimant may be a for medical, hospital and nursing ex pain and suffering loss of earnings an items may depend on what percentage disability is due to the accident and preexisting disease The physician ma be confronted with the difficult task timating this percentage

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